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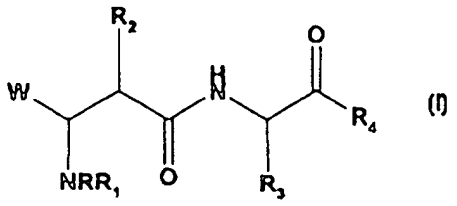

(I)

(57) Abstract

Succinic amide derivatives of formula (I), wherein W is a $-CO_2H$ or -CONHOH group; R, R_1 and R_2 are each hydrogen or an organic residue, R_3 is the residue of an alpha-aminoacid and R_4 is an organic group, are inhibitors of matrix metalloproteinases (MMPs) and of the release of tumor necrosis factor-alpha (TNF) from cells, and are therefore useful in the prevention, control and treatment of diseases in which MMPs or TNF are involved. A process for their preparation and pharmaceutical compositions containing them are also described.

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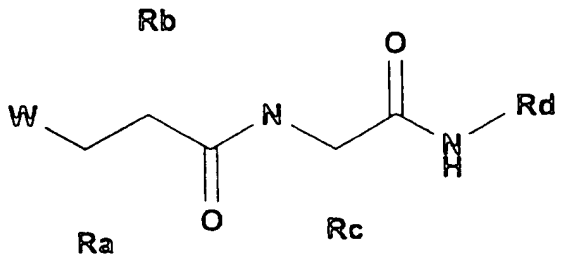
MATRIX METALLOPROTEINASE INHIBITORS

The present invention relates to new inhibitors of matrix metallo-proteinases (hereinafter MMPs), to a process for their preparation, to pharmaceutical compositions containing them, and to the use of such compounds in the prevention, control and treatment of diseases in which the proteolytic action of MMPs is involved. Furthermore, since the compounds herein described inhibit the release of tumor necrosis factor-alpha (hereinafter TNF) from cells, another object of the present invention is the use of pharmaceutical compositions containing said compounds for the treatment or prophylaxis of inflammatory, immunological or infectious diseases promoted by such cytokine.

Low molecular weight compounds able to inhibit one or more of the matrix metalloproteinases, in particular stromelysin-1 (MMP-3; EC 3.4.24.17), gelatinase A (MMP-2; EC 3.4.24.24), interstitial collagenase (MMP-1; EC 3.4.27.7), collagenase-2 (neutrophil collagenase; MMP-8), collagenase-3 (MMP-13), and the membrane-type metalloproteinases (in particular MT-MMP-1; MMP-14), are currently considered as promising therapeutic agents in degenerative, tumoral and autoimmune pathologies (e.g., P.D. Brown: "Matrix metalloproteinase inhibitors: A new class of anticancer agent", Curr. Opin. Invest. Drugs, 2:617-626, 1993; A. Krantz: "Proteinases in Inflammation", Annu. Rep. Med. Chem. 28:187-195, 1993). Many of such compounds described hitherto are peptide derivatives or pseudopeptides, bearing analogies to recognized peptide substrates of these enzymes, and characterized in addition by a functional group capable of binding the Zn (II) atom present in the catalytic site of said enzymes. Known classes of MMP inhibitors include those in which the Zn binding group is a carboxylic or hydroxamic acid, which is part of a (substituted) succinic moiety, in particular a succinic amide with an aminoacid, in turn derivatized as a primary or secondary amide, as the ones represented by the general formula (A)



(A)

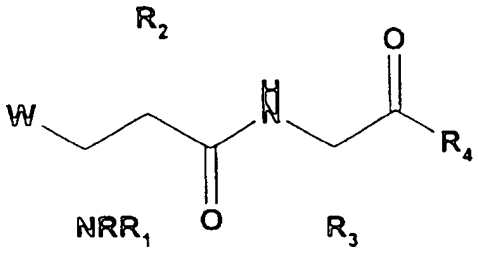
wherein W is $-CO_2H$ or -CONHOH, and R_a, R_b, R_c, and R_d are hydrogen atoms or appropriate substituents (e.g., N.R.A. Beeley et al., "Inhibitors of matrix metalloproteinases (MMP's)", Curr. Opin. Ther. Patents 4:7-16, 1994; J.R. Porter et al., "Recent developments in matrix metalloproteinase inhibitors", Exp. Opin. Ther. Patents 5:1287-1296, 1995; J.R. Morphy et al., "Matrix metalloproteinase inhibitors: Current status", Curr. Med. Chem. 2:743-762, 1995; R.P. Beckett et al., "Recent advances in matrix metalloproteinase research", DDT 1:16-26, 1996). Further, it is now recognized that compounds of the same general formula (A), wherein in particular W is -CONHOH, may be able to inhibit the release of TNF from the cell membrane anchored precursor, pro-TNF (e.g., G.M. McGeehan et al., "Regulation of tumour necrosis factor-alpha processing by a metalloproteinase inhibitor", Nature 370:558-561, 1994).

Although MMPs have been recognized as drug targets for at least 20 years, and MMP inhibitors encompassed by the general formula (A) have been disclosed since 1986 or before (e.g., see J.P. Dickens et al., U.S. Patent 4,599,361), no drug of this type has arrived the market yet. This is not because of questions about the therapeutic potential of MMP inhibitors, but because of problems of the "first generation" compounds, such as inhibitor potency, selectivity, aqueous solubility, duration of action in vivo, oral bioavailability, and potential toxicity (e.g., J.R. Porter, reference above; J. Hodgson, "Remodelling MMPIs", Biotechnology 13:554-557, 1995). Further, the precise role of each individual MMP in many disease states has not been completely elucidated. Thus, there is a strong need for better and diversified molecules, especially as far as the properties referred to above are concerned.

As stated above, an impressing number of MMP inhibitors of general formula (A) wherein W is -COOH or -CONHOH has been described in the literature, or in patents and published patent applications. Though referring to the common general structure (A), each disclosure is characterized by subtle variations in the nature of the R_a-R_d substituents. In fact, the balance of intrinsic level of activity, degree of specificity towards individual MMPs, and physicochemical and pharmacokinetic properties can vary in an unpredictable way as the substituents R_a-R_d are varied. Although a plethora of different possible values for R_b-R_d has been described, investigation on compounds of formula (A) wherein R_a is different from hydrogen has been very limited so far. In particular, the class of compounds of formula (A) wherein R_a is a heteroatom or a derivative thereof has almost no

precedent, a part the particular case of R_a being hydroxy, which includes a compound now under clinical development, British Biotechnology BB-2516 (also known as "marimastat"). We have now found a particular group of compounds of general formula (I), characterized by very potent biochemical activity against MMPs, in particular stromelysin(s), gelatinase(s) and collagenase(s), combined with physicochemical and pharmacokinetic properties which make such compounds suitable for their prospected use as drugs in the treatment of a variety of diseases in which uncontrolled activity of such MMPs is involved: further, we have found that many of such compounds effectively inhibit the release of TNF from its cell membrane precursor, pro-TNF: further, we have found a convenient and stereoselective method for their preparation from commercial intermediates.

The present invention provides compounds of formula (I),



(I)

wherein

W is a -COOH or -CONHOH group:

R is either hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl;

R_1 is either hydrogen or:

- lower alkyl, especially methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl; aryl, especially phenyl and naphthyl; and aryl-(lower alkyl), especially benzyl; these groups being either unsubstituted or substituted by one or more substituents, equal or different, selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group $-(CH_2)_m$-heterocyclyl or $-(CH_2)_m$-cyclopropyl, wherein m is either zero, or an integer from one to three, and heterocyclyl represents a 3 to 6 membered heterocyclyl ring, simple or condensed with a benzene or naphthalene ring, containing at least one nitrogen atom: still preferably succinimido, phthalimido, saccharin, hydantoin, indolyl, oxyindolyl,

2-oxo-isoindolinyl, imidazolyl, pyridyl, morpholino, pyrrolidino, 2-oxopyrrolidino, piperazino; and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-(CH_2)_nCOOH$ or a group $-(CH_2)_mCOOR^I$, wherein n may be 1, 2 or 3, m may be 0, 1, 2 or 3, and R^I is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, phenyl, benzyl, allyl, styryl, 1-naphthyl, 2-naphthyl, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group selected from $-(CH_2)_mSO_2R^I$, $-(CH_2)_mSO_2NH_2$, $-(CH_2)_mSO_2N(Me)_2$, $-(CH_2)_mSO_2NHR^I$, wherein m, R^I and possible substituents of such R^I group are as defined above, or a group $-(CH_2)_mSO_2$-(4-morpholino), $-(CH_2)_mSO_2$-(1-piperazino), $-(CH_2)_mSO_2$-(4-methyl-1-piperazino); or

- a group $-(CH_2)_nSO_3H$, wherein n is as defined above;

- acyl, especially acetyl, or benzoyl, or phenacetyl, either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}-C(O)R^{III}$, wherein $-R^{II}-$ is selected from a chemical bond, $-CH_2-$, $-CH_2(CH_2)_mCH_2-$ wherein m is as defined above, -CH=CH-, $-CH_2CH=CH-$, phenylene (i.e., $-C_6H_4-$), $-CH_2CH=CH-C_6H_4-$, $-CH_2CH_2CH=CH-$, $-CH_2-CC-$, $-CH_2CH_2-CC-$, $-CH_2CH_2CH=CH-C_6H_4-$, $-CH_2-CC-C_6H_4-$, $-CH_2CH_2-CC-C_6H_4-$, and R^{III} is selected from methyl, ethyl, phenyl, hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, and morpholino; or

- a group -C(O)-heterocyclyl, wherein heterocyclyl is as defined above, and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}$-heterocyclyl or $-C(O)-R^{II}$-aryl, wherein R^{II}, heterocyclyl, aryl and possible substituents of such heterocyclyl or aryl are as described above; or

R and R_1, taken together with the nitrogen atom to which they are attached, represent morpholino, pyrrolidino, piperazino, N-methylpiperazino, succinimido, or phthalimido;

R_2 is C_3 -C_{15} linear or branched alkyl, either unsubstituted or substituted by a C_3 -C_7 cycloalkyl group; or

R_2 is a group -R^{II}-H, wherein R^{II} is as defined above, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, C_3 -C_4 linear or branched alkyl, fluoro, chloro, C_1-C_4 alkoxy, nitro, amino, dimethylamino, carboxy, carboxymethyl; or

R_2 is a group -R^{II}-H, wherein R^{II} is as defined above, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, C_3 -C_4 linear or branched alkyl, fluoro, chloro, C_1-C_4 alkoxy, nitro, amino, dimethylamino, carboxy, carboxymethyl; or

R_2 is a group -R^{II}-X-R^{IV} , wherein R^{II} is as defined above, R^{IV} is C_1 -C_6 alkyl, C_2 -C_6 alkenyl, phenyl, phenyl (C_1 -C_6)alkyl, or phenyl (C_2 -C_6)alkenyl, either unsubstituted or substituted by a group selected from F, Cl, Br, C_1 -C_4 alkyl, C_1 -C_4 alkoxy, and X is either a direct bond, or an oxygen atom, a sulfur atom, or a sulfinyl -S(O)-, sulfonyl -$S(O)_2$ or carbamoyl group -CONH- or -NHCO-;

R_3 is the characterizing group of a natural or non-natural alpha-amino acid in which any functional group, if present, may be protected; including C_1 -C_9 straight or branched alkyl, C_2 -C_6 alkenyl, C_3 -C_7 cycloalkyl, phenyl, indolyl, naphthyl, adamantyl; or C_3 -C_7 cycloalkyl (C_1 -C_6) alkyl, phenyl (C_1 -C_6) alkyl, naphthyl (C_1 -C_6) alkyl, indolyl (C_1 -C_6) alkyl, wherein the alkyl, alkenyl, cycloalkyl, phenyl, indolyl and naphthyl groups may be substituted by ethyl, methyl, hydroxy, mercapto, carboxy, C_1 -C_6 alkoxy, phenoxy, benzyloxy, C_1 -C_6 alkylthio, phenylthio, benzylthio, C_1 -C_6 alkylsulfinyl, C_1 -C_6 alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, amino, mono-(C_1 -C_6) alkylamino, di- (C_1 -C_6) alkylamino, guanidino;

R_4 is either O-alkyl, wherein alkyl is a C_1 -C_4 straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 -C_4 straight or branched alkyl, chloro and methoxy; or

R_4 is -NH_2 , -NH(C_1 -C_6 alkyl), -NH-aryl, -NH-heterocyclyl; or

R_4 is -NH(C_1 -C_6 alkyl) substituted by phenyl or heterocyclyl; or

R_4 is -NH(C_2 -C_6 alkyl) substituted by a group selected from -$CONH_2$, -$NHCONH_2$, -SO_2NH_2 , -$NHSO_2NH_2$, or derivatives thereof wherein the terminal nitrogen atom is substituted by one or two methyl groups, or derivatives thereof wherein the terminal nitrogen atom is part of a morpholino, pyrrolidino, piperazino, or N-methylpiperazino

ring; or

R_4 is -NH(C_2 -C_6 alkyl) substituted by amino, protected amino, mono (C_1-C_6) alkylamino, di (C_1 -C_6) alkylamino, guanidino, morpholino, piperazino or N-methylpiperazino; or

R_3 and R_4 taken together are a group of the formula -$(CH_2)_m$-NH- , where m is from 5 to 12, optionally interrupted by a -NR_5 - group, wherein R_5 is selected from hydrogen, C_1 -C_6 alkyl, C_1 -C_6 alkoxycarbonyl, aryl, aryl (C_1 -C_6)alkyl, or aryl (C_1 -C_6) alkoxycarbonyl, or interrupted by a group -C_6H_4-O- , or interrupted by an indole ring linked through its C-3 and nitrogen atoms;

and wherein the alkyl, alkenyl, phenyl, benzyl, cycloalkyl, heterocyclyl, phenyl (C_1 -C_6)alkyl, phenyl (C_2 -C_6)alkenyl, heterocyclyl (C_1 -C_6)alkyl, cycloalkyl (C_1 -C_6)alkyl in any of the above definitions of R, R_1 , R_2 , R_3 , R_4 and A are either unsubstituted or substituted by one or more substituents, as specified below;

and the salts, solvates and hydrates thereof,

with the proviso that, when -NRR_1 is -NH_2, protected amino or acylamino, R_3 is tert-butyl and R_4 is either amino or alkylamino, then R_2 is different from isobutyl.

As used herein the term "alkyl" refers to a straight or branched chain alkyl moiety having from 1 to 9 carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl and so on.

The term "alkenyl" refers to a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms and having in addition one double bond of either E or Z stereochemistry where applicable. Examples of alkenyl groups are: vinyl, allyl, 1-propenyl, 1-butenyl, 2-butenyl , metallyl, crotyl and so on.

The term "aryl" refers to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms, such as phenyl, naphthyl, indanyl.

The term "cycloalkyl" refers to a saturated carbocyclic group of 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

The term "heterocyclyl" refers to a 3- to 7-membered, saturated or unsaturated heterocyclyl ring, containing at least one heteroatom selected from O, S and N, wherein any ring nitrogen may be oxidized as an N-oxide, any ring carbon may be oxidized as a carbonyl, and any ring sulfur may be oxidized as a sulfoxide or sulfone; and wherein said heterocyclyl ring may be optionally fused to a second 5- or 6-membered , saturated or unsaturated heterocyclyl ring, or to a C_3 -C_7 cycloalkyl ring, or to a benzene or

naphthalene ring. Examples of heterocyclyl groups are pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, thienyl, furyl, aziridinyl, oxiranyl, azetidinyl, succinimido, pyridyl, pyrazinyl, pyrimidinyl, pyranyl, pyridazinyl, hydantoinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, azepinyl and so on.

When in the definition of "aryl" and "heterocyclyl" above such aryl or heterocyclyl groups are fused to a second ring, the latter may be either phenyl, C_4 -C_7 cycloalkyl, or a 3- to 7-membered, saturated or unsaturated heterocyclyl ring, containing one to three heteroatoms selected from O, S and N, wherein any ring nitrogen may be oxidized as an N-oxide, any ring carbon may be oxidized as a carbonyl, and any ring sulfur may be oxidized as a sulfoxide or sulfone. Examples of such such fused aryl or heterocyclyl groups are benzothienyl, benzothiazolyl, benzoxazolyl, isobenzofuranyl, benzofuranyl, chromenyl, indolyl, oxindolyl, phthalimido, quinolyl, isoquinolyl, indolizinyl, isoindolyl, 2-oxoisoindolyl, saccarinyl, cinnolinyl, indazolyl, purinyl, cyclopentylphenyl, cyclohexylphenyl, cyclopentylpyridyl, 1,3-benzodioxole and so on. Such bicyclyc rings can be attached to the rest of the molecule either at one or at the other ring atom consitituents: for example, a cyclohexylpyridyl substituent includes both a cyclohexyl group fused to a pyridyl ring, and a pyridyl group fused to a cyclohexyl ring.

The term "side chain of a naturally occurring α-amino acid" encompasses the side chains of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, and penicillamine.

The term "side chain of a non-natural α-amino acid" encompasses the side chain of known α-amino acids not belonging to the category of "naturally occurring α-amino acid", such as α-amino-*n*-butyric acid, α-amino-*n*-pentanoic acid, α-amino-*n*-hexanoic acid, α-amino-*neo*hexanoic acid, α-amino-*neo*heptanoic acid, S-methyl penicillamine and its sulfoxides and sulfone, tert-butylglycine, phenylglycine, (diphenylmethyl)glycine, cyclohexylalanine, homophenylalanine, homocysteine, homoserine, alloisoleucine, allothreonine, 3,4-dihydroxyphenylalanine, 5-hydroxylysine, 4-hydroxyproline, ornithine and the like.

Substituents which may be present in the above said alkyl, alkenyl, phenyl, benzyl, cycloalkyl, heterocyclyl, phenyl (C_1 -C_6)alkyl, phenyl (C_2 -C_6)alkenyl, heterocyclyl (C_1 -

C_6)alkyl, cycloalkyl (C_1 -C_6)alkyl in any of the above definitions of R, R_1, R_2, R_3, R_4 and A are selected from the following ones:

- halo (i.e., fluoro, bromo, chloro or iodo);
- hydroxy;
- nitro;
- azido;
- mercapto (i.e., -SH), and acetyl or phenylacetyl esters thereof (i.e., $-SCOCH_3$ and $-SCOCH_2C_6H_5$);
- amino (i.e., $-NH_2$ or $-NHR^V$ or $-NR^VR^{VI}$, wherein R^V and R^{VI}, which are the same or different, are straight or branched C_1-C_6 alkyl group, phenyl optionally substituted with C_1-C_6 alkyl or phenyl(C_1-C_6 alkyl) groups; or R^V and R^{VI} taken together with the nitrogen atom form a ring such as piperidino, morpholino or pyrrolidino or piperazino group, and may be optionally substituted by any of the substituents herein listed);
- guanidino, i.e., $-NHC(=NH)NH_2$;
- formyl (i.e. -CHO);
- cyano;
- carboxy (i.e. -COOH), or esters thereof (i.e., $-COOR^V$), or amides thereof (i.e., $-CONR^VR^{VI}$), wherein R^V and R^{VI} are as defined above, and including morpholino-amides, pyrrolidino-amides, and carboxymethylamides $-CONHCH_2COOH$;
- sulfo (i.e., $-SO_3H$);
- acyl, i.e., $-C(O)R^V$, wherein R^V is as defined above, including monofluoroacetyl, difluoroacetyl, trifluoroacetyl;
- carbamoyloxy (i.e., $-OCONH_2$) and N-methylcarbamoyloxy;
- acyloxy, i.e., $-OC(O)R^V$ wherein R^V is as defined above, or formyloxy;
- acylamino, i.e., $-NHC(O)R^V$, or $-NHC(O)OR^V$, wherein R^V is as defined above or it is a group $-(CH_2)_tCOOH$ where t is 1, 2 or 3;
- ureido, i.e., $-NH(CO)NH_2$, $-NH(CO)NHR^V$, $-NH(CO)NR^VR^{VI}$, wherein R^V and R^{VI} are as defined above, including -NH(CO)-(4-morpholino), -NH(CO)-(1-pyrrolidino), -NH(CO)-(1-piperazino), -NH(CO)-(4-methyl-1-piperazino);
- sulfonamido, i.e., $-NHSO_2R^V$ wherein R^V is as defined above;
- a group $-(CH_2)_tCOOH$, and esters and amides thereof, i.e., $-(CH_2)_tCOOR^V$ and

$-(CH_2)_tCONH_2$, $-(CH_2)_tCONHR^V$, $-(CH_2)_tCONR^VR^{VI}$, wherein t, R^V and R^{VI} are as defined above;

- a group $-NH(SO_2)NH_2$, $-NH(SO_2)NHR^V$, $-NH(SO_2)NR^VR^{VI}$, wherein R^V and R^{VI} are as defined above, including -NH(SO$_2$)-(4-morpholino), -NH(SO$_2$)-(1-pyrrolidino), -NH(SO$_2$)-(1-piperazino), -NH(SO$_2$)-(4-methyl-1-piperazino);

- a group $-OC(O)OR^V$, wherein R^V is as defined above;

- a group $-OR^V$, wherein R^V is as defined above, including $-OCH_2COOH$;

- a group $-SR^V$, wherein R^V is as defined above, including $-SCH_2COOH$;

- a group $-S(O)R^V$, wherein R^V is as defined above;

- a group $-S(O_2)R^V$, wherein R^V is as defined above;

- a group $-SO_2NH_2$, $-SO_2NHR^V$, or $-SO_2NR^VR^{VI}$, wherein R^V and R^{VI} are as defined above;

- C_1 -C_6 alkyl or C_2 -C_6 alkenyl;

- C_3 -C_7 cycloalkyl;

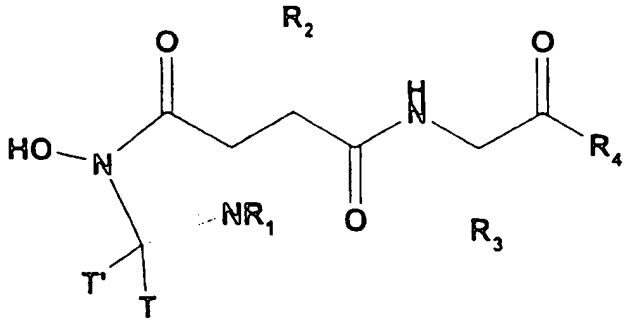
- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl, cyanomethyl, carboxymethyl, sulfomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl, alkoxycarbonylmethyl, guanidinomethyl.

When present carboxy, hydroxy, thiol and amino groups may be either free or in a protected form. Protected forms of said groups are any of those generally known in the art, as described, for example, by T.W. Greene in "Protective Groups in Organic Chemistry", Wiley Interscience. Preferably, carboxy groups are protected as esters thereof, in particular methyl, ethyl, tert-butyl, benzyl, and 4-nitrobenzyl esters. Hydroxy, thiol and amino groups, when protected, are preferably in the form of esters, thioesters, and amide derivatives, respectively, e.g. as acetates, thioacetates, acetamides.

The present invention provides the salts of those compounds of formula (I) that have salt-forming groups, especially the salts of the compounds having a carboxylic group, a N-hydroxycarbamoyl group, and a sulfo group, or the salts of the compounds having a basic group, especially an amino or guanidino group. The salts are especially physiologically tolerable salts, for example alkali metal and alkaline earth metal salts (e.g. sodium, potassium, lithium, calcium and magnesium salts), ammonium salts and salts with an appropriate organic amine or amino acid (e.g. arginine, procaine salts), and the addition

salts formed with suitable organic or inorganic acids (e.g. hydrochlorides, hydrobromides, sulfates, phosphates) or carboxylic and sulfonic organic acids (e.g. acetates, citrates, succinates, malonates, lactates, tartrates, fumarates, maleates, methanesulphonates, *p*-toluenesulphonates). Some compounds of formula (I) which contain a carboxylate and an ammonium group may exist as zwitterions; such salts are also part of the present invention.

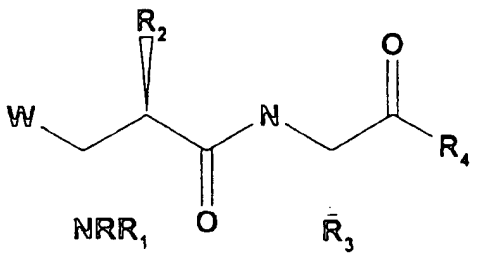
Furthermore, hydrates, solvates of compounds of formula (I), and physiologically hydrolyzable derivatives (i.e., prodrugs) of compounds of formula (I) are included within the scope of the present invention. Particularly preferred prodrugs of the compounds of formula (I) are ester derivatives. They include esters of compounds of formula (I) wherein W is -COOH, or wherein a carboxy group is present in any of the substituents R, R_1 -R_4, which are obtained by condensation of such carboxy group with a pharmaceutically acceptable alcohol, e.g. ethanol; or esters of compounds of formula (I) wherein a hydroxy group is present in any of the substituents R, R_1 -R_4, which are obtained by condensation of such hydroxy group with a pharmaceutically acceptable carboxylic acid, e.g. acetic acid, pivalic acid, benzoic acid and the like. Other particularly preferred prodrugs within the present invention are the cyclic condensation products between compounds of formula (I) wherein W is -CONHOH and R is hydrogen and a pharmacautically acceptable aldehyde of general formula T-CHO or a ketone of general formula TT'CO, wherein T and T' are carbon radicals, such as lower alkyl, phenyl, benzyl. Such condensation products, which are represented herebelow, are obtained by mixing the two components, and removing water by evaporation.



The present invention also includes, within its scope, pharmaceutical compositions comprising one or more of the compounds (I) as active ingredients, in association with

pharmaceutically acceptable carriers, excipients or other additives, if desirable.

Preferred compounds within the present invention have the structure (I'):



(I')

wherein:

W is a -COOH or -CONHOH group;

R is either hydrogen, methyl, ethyl, or benzyl;

R_1 is either hydrogen or:

- lower alkyl, especially methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl; aryl, especially phenyl and naphthyl; and aryl-(lower alkyl), especially benzyl; these groups being either unsubstituted or substituted by one or more substituents, equal or different, selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group $-(CH_2)_m$-heterocyclyl or $-(CH_2)_m$-cyclopropyl, wherein m is either zero, or an integer from one to three, and heterocyclyl represents a 3 to 6 membered heterocyclyl ring, simple or condensed with a benzene or naphthalene ring, containing at least one nitrogen atom; still preferably succinimido, phthalimido, saccharin, hydantoin, indolyl, oxyindolyl, 2-oxo-isoindolinyl, imidazolyl, pyridyl, morpholino, pyrrolidino, 2-oxopyrrolidino, piperazino; and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-(CH_2)_nCOOH$ or a group $-(CH_2)_mCOOR^1$, wherein n may be 1, 2 or 3, m may be 0, 1, 2 or 3, and R^1 is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, phenyl, benzyl, allyl, styryl, 1-naphthyl, 2-naphthyl, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group $-(CH_2)_mCONH_2$ or $-(CH_2)_mCON(CH_3)_2$ or $-(CH_2)_mCONHR^I$, wherein m, R^I and possible substituents of such R^I group are as defined above, or a group $-(CH_2)_m$-CO-(4-morpholino), $-(CH_2)_m$-CO-(1-piperazino), and $-(CH_2)_m$-CO-(4-methyl-1-piperazino); or

- a group selected from $-(CH_2)_mSO_2R^I$, $-(CH_2)_mSO_2NH_2$, $-(CH_2)_mSO_2N(Me)_2$, $-(CH_2)_mSO_2NHR^I$, wherein m, R^I and possible substituents of such R^I group are as defined above, or a group $-(CH_2)_mSO_2$-(4-morpholino), $-(CH_2)_mSO_2$-(1-piperazino), $-(CH_2)_mSO_2$-(4-methyl-1-piperazino); or

- a group $-(CH_2)_nSO_3H$, wherein n is as defined above;

- acyl, especially acetyl, or benzoyl, or phenacetyl, either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}-C(O)R^{III}$, wherein $-R^{II}-$ is selected from a chemical bond, $-CH_2-$, $-CH_2(CH_2)_mCH_2-$ wherein m is as defined above, $-CH=CH-$, $-CH_2CH=CH-$, phenylene (i.e., $-C_6H_4-$), $-CH_2CH=CH-C_6H_4-$, $-CH_2CH_2CH=CH-$, $-CH_2-CC-$, $-CH_2CH_2-CC-$, $-CH_2CH_2CH=CH-C_6H_4-$, $-CH_2-CC-C_6H_4-$, $-CH_2CH_2-CC-C_6H_4-$, and R^{III} is selected from methyl, ethyl, phenyl, hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, and morpholino; or

- a group -C(O)-heterocyclyl, wherein heterocyclyl is as defined above, and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}$-heterocyclyl or $-C(O)-R^{II}$-aryl, wherein R^{II}, heterocyclyl, aryl and possible substituents of such heterocyclyl or aryl are as described above; or

R and R_1, taken together with the nitrogen atom to which they are attached, represent morpholino, pyrrolidino, piperazino, N-methylpiperazino, succinimido, or phthalimido;

R_2 is C_3 -C_{15} linear or branched alkyl, either unsubstituted or substituted by a C_3 -C_7 cycloalkyl group; or

R_2 is a group $-R^{II}-H$, wherein R^{II} is as defined above, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, C_3 -C_4 linear or branched alkyl, fluoro, chloro, C_1-C_4 alkoxy, nitro, amino, dimethylamino, carboxy, carboxymethyl; or

R_2 is a group $-R^{II}-X-R^{IV}$, wherein $-R^{II}-$ is as defined above, -X- is either a direct bond, -O-, -S-, -SO-, $-SO_2-$, -CONH- or -NHCO-, and R^{IV} is either C_1 -C_6 alkyl, C_2 -C_6 alkenyl, methyl, ethyl, propyl, butyl, phenyl or benzyl, the benzene ring of the phenyl and benzyl groups being either unsubstituted or substituted by one or more substituents selected from methyl, ethyl, propyl, butyl, hydroxy, methoxy, ethoxy, chloro, fluoro, trifluoromethyl or nitro;

R_3 is phenylmethyl, cyclohexylmethyl, isobutyl, tert-butyl, $-C(CH_3)_2C_6H_5$, $-C(CH_3)_2OCH_3$, $-C(CH_3)_2SCH_3$, $-C(CH_3)_2SOCH_3$, $-C(CH_3)_2SO_2CH_3$, $-CH(C_6H_5)_2$, $-CH(CH_3)OH$, $-CH(CH_3)OMe$, $-CH(CH_3)O$-isopropyl, $-CH(CH_3)O$-tert-butyl, $-CH(CH_3)OPh$, $-CH(CH_3)OCH_2Ph$, (4-methoxy)phenylmethyl, (4-hydroxy)phenylmethyl, indolylmethyl, (N-methyl)indolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, (4-carboxymethoxy)phenylmethyl, cyclohexyl, phenyl, pyridyl, thiazolyl, thienyl, pyridylmethyl, thiazolylmethyl, thienylmethyl, and derivatives thereof wherein any phenyl, pyridyl, thiazolyl and thienyl group is substituted by chloro, fluoro, methoxy or C_1 -C_3 alkyl;

R_4 is either O-alkyl, wherein alkyl is a C_1 -C_4 straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 -C_4 straight or branched alkyl, chloro and methoxy; or

R_4 is $-NH_2$, or -NH-alkyl, wherein alkyl is selected from methyl, ethyl, propyl, butyl, isopropyl, iso-butyl, sec-butyl, tert-butyl; such linear or branched alkyl groups being either unsubstituted, or substituted by a group selected from phenyl, benzyl, 2-pyridyl, 3-pyridyl, 1,3,4-thiadiazolyl-2-yl, 2-thiazolyl, these groups in turn being either unsubstituted or substituted by a substituent selected from methyl, ethyl, methoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, ethoxycarbonyl, $-SO_2NH_2$, $-SO_2NHC_6H_5$, $-SO_2$-morpholino, $-SO_2CH_3$, $-CONH_2$, -CO-morpholino; or

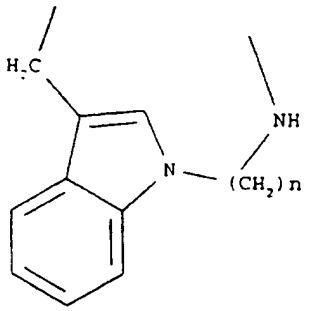
R_4 is a group $-NHCH_2CH_2Y$, $-NHCH_2CH_2CH_2Y$, $-NHCH_2CH_2CH_2CH_2Y$, $-NHCH_2CH(CH_3)Y$, or $-NHCH_2C(CH_3)_2Y$, wherein Y is amino, methylamino, dimethylamino, morpholino, pyrrolidino, piperazino, N-methylpiperazino, hydroxy, methoxy, ethoxy, methylthio, 2-(dimethylamino)ethylthio, 2-(morpholino)ethylthio, Cl, F, Br, phenoxy or phenylthio, wherein the phenyl ring may be substituted by hydroxy or methoxy; or

R_4 is a -NH-aryl, -NH-heterocyclyl, -NH-CH_2-aryl, -NH-$(CH_2)_2$aryl, -NH-CH_2-heteroaryl, or -NH-$(CH_2)_2$-heterocyclyl wherein the aryl group is selected from phenyl, 4-fluorophenyl, 4-methoxyphenyl, 1,3-benzodioxolyl, 4-tolyl, 1-indanyl, 5-indanyl, and the heterocyclyl group is selected from 2-benzimidazolyl, 2-benzothiazolyl, 1-benzotriazolyl, 2,5-dimethyl-1-pyrrolidinyl, 2,6-dimethylpiperidinyl, 2-imidazolyl, 1-indolyl, 5-indolyl, 5-indazolyl, 1-isoquinolyl, 5-isoquinolyl, 2-methoxy-5-pyridyl, 1-methyl-2-benzimidazolyl, 4-methyl-7-coumarinyl, 3-methyl-5-isothiazolyl, 5-methyl-3-isoxazolyl, pyrazinyl, 3-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 3-quinolyl, 5-tetrazolyl, 1-methyl-5-tetrazolyl, 1,3,4-thiadiazol-2-yl, 2-thiazolyl, 1,2,4-triazin-3-yl, and 1,2,4-triazol-3-yl; or

R_4 is -NH(C_2 -C_6 alkyl), wherein the alkyl group is substituted by a substituent selected from -$CONH_2$, -CONHMe, -$NHCONH_2$, -$NHCONMe_2$, -NHCO-(4-morpholino), -NHCO-(4-methyl-1-piperazino), -$NHSO_2NH_2$, -$NHSO_2NMe_2$, -$NHSO_2$-(4-morpholino), and -$NHSO_2$-(4-methyl-1-piperazino); or

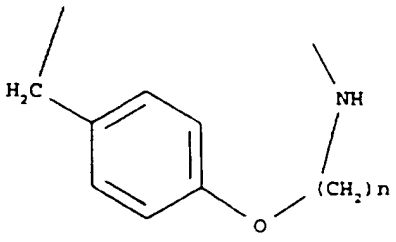
R_3 and R_4 taken together are a group of the formula -$(CH_2)_{10}$-NH-, or a group of the formula -$(CH_2)_4$-NH-$(CH_2)_5$-NH- ; or

R_3 and R_4 taken together are a group of the formula (B) hereinbelow:



(B)

or a group of the formula (C) hereinbelow:



(C)

wherein n is an integer from 3 to 6;

and the pharmaceutically acceptable salts, solvates, hydrates, or prodrug thereof, as above described.

with the proviso that, when $-NRR_1$ is $-NH_2$, protected amino or acylamino, R_3 is tert-butyl and R_4 is either amino or alkylamino, then R_2 is different from isobutyl.

A preferred group of compounds within the present invention encompasses compounds of formula (I') wherein:

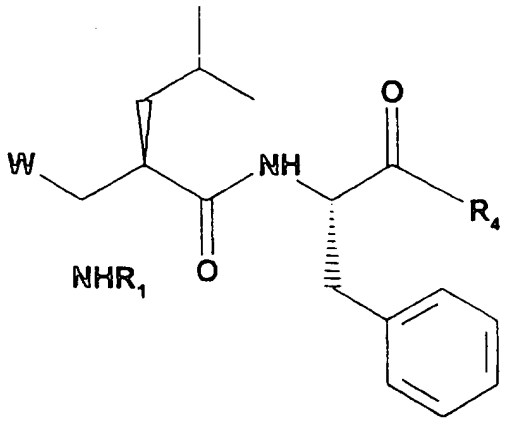
R_2 is isobutyl;

R_3 is phenylmethyl;

and W, R, R_1 and R_4 are as defined above.

Representative examples within this particularly preferred group of compounds are those listed in Table I herebelow:

Table I.



#	W	R_1	R_4
I-1	COOH	H	NHMe
I-2	CONHOH	H	NHMe
I-3	CONHOH	H	NH-iBu
I-4	CONHOH	CH_2-C_6H_4-F	NHMe
I-5	CONHOH	H	$NHCH_2CH_2Ph$
I-6	CONHOH	H	$NHCH_2CH_2$ -morpholino
I-7	CONHOH	H	$NHCH_2CH_2COOMe$
I-8	CONHOH	H	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-9	CONHOH	H	$NHCH_2COOEt$
I-10	CONHOH	H	$NHCH(CHMe_2)COOH$
I-11	CONHOH	H	$NHCH_2CH_2COOH$
I-12	CONHOH	H	$NHCH_2Ph$
I-13	CONHOH	H	$NHCH_2$-(3-pyridyl)
I-14	CONHOH	H	$NH(CH_2)_4NMe_2$
I-15	CONHOH	H	$NHCH_2CH_2OC_6H_4$-*p*-OMe
I-16	CONHOH	Me	NH-tBu
I-17	CONHOH	C_6H_4-*p*-OMe	NHMe
I-18	CONHOH	CH_2-C_6H_4-*p*-OMe	NH-CH_2-(3-pyridyl)
I-19	CONHOH	H	NH-CH_2- (2-thiazolyl)
I-20	CONHOH	H	NH-CH_2-(5-methyl-1,3,4-thiadiazol-2-yl)

I-21	CONHOH	H	NH-tBu
I-22	CONHOH	H	$NHCH_2CMe_2OH$
I-23	CONHOH	H	$NHCH_2CH_2NH_2$
I-24	COOH	$COOCMe_3$	NHMe
I-25	CONHOH	$COOCMe_3$	NHMe
I-26	CONHOH	$COOCMe_3$	$NHCH_2CH_2$ -morpholino
I-27	CONHOH	$COOCMe_3$	$NHCH_2CH_2CO$-morpholino
I-28	CONHOH	$COOCMe_3$	$NHCH_2CH_2SO_2$-morpholino
I-29	COOH	$COOCMe_3$	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-30	CONHOH	$COOCMe_3$	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-31	COOH	$COOCMe_3$	NH_2
I-32	CONHOH	$COOCMe_3$	NH_2
I-33	CONHOH	$COOCMe_3$	$NH(CH_2)_3CONH_2$
I-34	CONHOH	$COOCMe_3$	$NHCH_2CH_2COOH$
I-35	CONHOH	$COOCMe_3$	$NH(CH_2)_4NMe_2$
I-36	CONHOH	$COOCMe_3$	$NHCH_2CH_2SCH_2CH_2$-morpholino
I-37	CONHOH	$COOCMe_3$	$NHCH_2CH_2SCH_2CH_2NMe_2$
I-38	CONHOH	$COOCMe_3$	$NHCH_2CH_2SMe$
I-39	CONHOH	$COOCMe_3$	$NHCH_2CH_2NMe_2$
I-40	CONHOH	$COOCMe_3$	$NHCH_2CH_2OMe$
I-41	CONHOH	$COOCMe_3$	$NH(CH_2)_4$-morpholino
I-42	CONHOH	$COOCMe_3$	$NHCH_2CH_2NHSO_2$-morpholino
I-43	COOH	$SO_2C_6H_4$-*p*-Me	NHMe
I-44	CONHOH	$SO_2C_6H_4$-*p*-Me	NHMe
I-45	CONHOH	$SO_2C_6H_4$-*p*-Me	NH_2
I-46	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2$-morpholino
I-47	CONHOH	$SO_2C_6H_4$-*p*-Me	$NH(CH_2)_4$-morpholino
I-48	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2COOH$
I-49	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH(CMe_3)COOH$
I-50	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2$-(3-pyridyl)
I-51	CONHOH	$SO_2C_6H_4$-*p*-OMe	$NHCH_2CH_2$-morpholino

I-52	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2CO$-morpholino
I-53	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-54	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2NMe_2$
I-55	CONHOH	$CONHCH_2Ph$	NHMe
I-56	CONHOH	$CONHCH_2Ph$	$NHCH_2CH_2$-morpholino
I-57	CONHOH	CONHMe	NHMe
I-58	CONHOH	$CONMe_2$	NHMe
I-59	CONHOH	$CONH_2$	NHMe
I-60	COOH	CO-morpholino	NHMe
I-61	CONHOH	CO-morpholino	NHMe
I-62	CONHOH	CO-morpholino	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-63	CONHOH	CO-morpholino	NH-tBu
I-64	COOH	$COOCH_2Ph$	NHMe
I-65	CONHOH	$COOCH_2Ph$	NHMe
I-66	CONHOH	$COCH_3$	NHMe
I-67	CONHOH	$COCH_2CH_2COOMe$	NHMe
I-68	CONHOH	$COCH_2CH_2COOH$	NHMe
I-69	CONHOH	$COCH_2CH_2COOH$	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
I-70	CONHOH	$COCH_2CH_2CONH_2$	NHMe
I-71	COOH	COPh	NHMe
I-72	CONHOH	COPh	NHMe
I-73	CONHOH	$COCH_2Ph$	NHMe
I-74	CONHOH	$COCH_2C_6H_4$-*p*-COMe	NHMe
I-75	CONHOH	COC_6H_4-*p*-NHAc	NHMe
I-76	CONHOH	COC_6H_4-*o*-OAc	NHMe
I-77	CONHOH	COC_6H_4-*o*-COOH	NHMe
I-78	CONHOH	COC_6H_4-*p*-COOH	NHMe
I-79	CONHOH	$COCH_2$-(1-phthalimido)	NHMe
I-80	CONHOH	$COCH_2$-(*N*-saccharinyl)	NHMe
I-81	CONHOH	$COCH_2$-(5-hydantoinyl)	NHMe
I-82	CONHOH	$COCH_2$-(3-methyl-1-hydantoinyl)	NHMe

I-83	CONHOH	$COCH_2$-(3-benzyl-1-hydantoinyl)	NHMe
I-84	CONHOH	$COCH_2$-(1-hydantoinyl)	NHMe
I-85	CONHOH	$COCH_2$-(3-hydantoinyl)	NHMe
I-86	CONHOH	$COCH_2$-(1,5,5-trimethyl-3-hydantoinyl)	NHMe
I-87	CONHOH	$COCH_2CH_2OH$	NHMe
I-88	CONHOH	$COCH_2NH_2$	NHMe
I-89	CONHOH	$COCH_2NHAc$	NHMe
I-90	CONHOH	$COCH_2CH(NHCOOCMe_3)COOH$	NHMe
I-91	CONHOH	$COCH(CH_3)NHAc$	NHMe
I-92	CONHOH	prolyl	NHMe
I-93	CONHOH	3-hydroxyprolyl	NHMe
I-94	COOH	CO-(2-pyridyl)	NHMe
I-95	CONHOH	CO-(2-pyridyl)	NHMe
I-96	CONHOH	CO-(3-pyridyl)	NHMe
I-97	CONHOH	CO-(2-thienyl)	NHMe
I-98	CONHOH	benzoyl	NHMe
I-99	CONHOH	CO-(2-acetoxyphenyl)	NHMe
I-100	CONHOH	trifluoroacetyl	NHMe
I-101	CONHOH	SO_2CF_3	NHMe
I-102	CONHOH	SO_2Me	NHMe
I-103	CONHOH	SO_2Me	$NHCH_2CH_2$-morpholino
I-104	CONHOH	SO_2-CH=CH-C_6H_4-*p*-Me	$NHCH_2CH_2$-morpholino
I-105	CONHOH	SO_2-morpholino	NHMe
I-106	CONHOH	Me	NHMe
I-107	CONHOH	CH_2Ph	NHMe
I-108	CONHOH	H	NH-isopropyl
I-109	CONHOH	H	$NHCH_2$-(2-pyridyl)
I-110	CONHOH	$COOCMe_3$	$NHCH_2$-(2-pyridyl)
I-111	CONHOH	H	$NHCH_2$-(3-pyridyl)
I-112	CONHOH	$COOCMe_3$	$NHCH_2$-(3-pyridyl)
I-113	CONHOH	H	$NHCH_2CH_2NHCO$-(morpholino)

I-114	CONHOH	$COOCMe_3$	$NHCH_2CH_2NHCO$-(morpholino)
I-115	CONHOH	H	$NHCH_2CH_2NHSO_2$-(morpholino)
I-116	CONHOH	$COOCMe_3$	$NHCH_2CH_2NHSO_2$-(morpholino)
I-117	CONHOH	CO-morpholino	$NHCH_2CH_2NHSO_2$-(morpholino)
I-118	CONHOH	H	$NHCH_2CH_2NHSO_2$-(4-methylpiperazino)
I-119	CONHOH	$COOCMe_3$	$NHCH_2CH_2NHSO_2$-(4-methylpiperazino)
I-120	CONHOH	$SO_2C_6H_4$-*p*-Me	$NHCH_2CH_2NHSO_2$-(4-methylpiperazino)

Another preferred group of compounds within the present invention encompasses compounds of formula (I') wherein:

R_2 is isobutyl;

R_3 is 4-fluorophenylmethyl, 4-hydroxyphenylmethyl, 4-methoxyphenylmethyl; or

R_3 is selected from phenyl, pyridyl, thiazolyl, thienyl, pyridylmethyl, thiazolylmethyl, thienylmethyl, quinolylmethyl, isoquinolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, indolylmethyl, N-methylindolylmethyl, imidazolylmethyl, including derivatives thereof substituted at the phenyl, pyridyl, thiazolyl, thienyl, quinolyl or isoquinolyl ring by one or two substituents selected from chloro, fluoro, hydroxy, methoxy, methyl, ethyl, t-butyl, -OCH_2COOH; or

R_3 is cyclohexyl or cyclohexylmethyl; or

R_3 is selected from -$C(CH_3)_2OCH_3$, -$C(CH_3)_2SCH_3$, -$C(CH_3)_2SOCH_3$, -$C(CH_3)_2SO_2CH_3$, -$CH(CH_3)OH$, -$CH(CH_3)OMe$, -$CH(CH_3)O$-isopropyl, -$CH(CH_3)O$-tert-butyl, -$C(CH_3)_2CH_2OH$, -$(CH_2)_3OH$; or

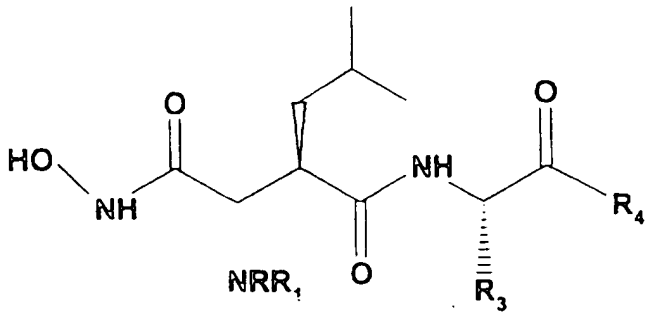
R_3 is a group a group selected from -$CH(C_6H_5)_2$, -$C(CH_3)_2C_6H_5$, -$CH(CH_3)OPh$, -$CH(CH_3)OCH_2Ph$, including derivatives thereof substituted at the phenyl ring(s) by one or two substituents selected from chloro, fluoro, hydroxy, methoxy, methyl, ethyl, propyl or t-butyl; or

R_3 and R_4 taken together constitute a group of the formula -$(CH_2)_{10}$-NH-, or a group of formula (B) or (C) above, wherein n is 6;

and W, R, R_1 and R_4 are as defined above.

Representative examples within this particularly preferred group of compounds are those listed in Table II herebelow:

Table II.



#	NRR_1	R_3	R_4
II-1	NH_2	$CH_2C_6H_4$-*p*-OMe	NHMe
II-2	NH_2	$CHPh_2$	NH_2
II-3	NH_2	$C(Me)_2SMe$	NHMe
II-4	$NHCOOCMe_3$	$C(Me)_2SMe$	NHMe
II-5	NH_2	$C(Me)_2SOMe$	NHMe
II-6	NH_2	$C(Me)_2SO_2Me$	NHMe
II-7	$NHCOOCMe_3$	$C(Me)_2SO_2Me$	NHMe
II-8	NH_2	$CH_2C_6H_{11}$	$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
II-9	NH_2	$C(Me)_2SMe$	NH-tBu
II-10	NH_2	$C(Me)_2SMe$	NH-$(CH_2)_2$-C_6H_4-*p*-SO_2NH_2
II-11	NHMe	$C(Me)_2SMe$	NH-tBu
II-12	NH_2	$C(Me)_2SMe$	NH(2-pyridylmethyl)
II-13	$NHCOOCMe_3$	$C(Me)_2SMe$	NH(2-pyridylmethyl)
II-14	NH_2	$C(Me)_2SMe$	NH(3-pyridylmethyl)
II-15	$NHCOOCMe_3$	$C(Me)_2SMe$	NH(3-pyridylmethyl)
II-16	$NHCOOCMe_3$	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
II-17	$NHSO_2Me$	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
II-18	$NHSO_2Me$	$C(Me)_2SMe$	NH(3-pyridylmethyl)
II-19	$NHSO_2C_6H_4$-*p*-Me	$C(Me)_2SMe$	NH_2

	II-20	$NHSO_2C_6H_4$-*p*-Me	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-21	$NHSO_2C_6H_4$-*p*-Me	$C(Me)_2SMe$	NH(3-pyridylmethyl)
	II-22	NHCOMe	$C(Me)_2SMe$	NHMe
	II-23	NHCOMe	$C(Me)_2SMe$	NH(3-pyrydylmethyl)
5	II-24	NHCO-morpholino	$C(Me)_2SMe$	NHMe
	II-25	NHCO-morpholino	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-26	NHCO-morpholino	$C(Me)_2SMe$	NH(3-pyridylmethyl)
	II-27	NHMe	$C(Me)_2SMe$	NHMe
	II-28	NMe_2	$C(Me)_2SMe$	NHMe
10	II-29	$NHCOCH_2CH_2CONH_2$	$C(Me)_2SMe$	NHMe
	II-30	$NHCOCH_2CH_2CONH_2$	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-31	$NHCOCH_2CH_2CONH_2$	$C(Me)_2SMe$	NH(3-pyridylmethyl)
	II-32	4-morpholinyl	$C(Me)_2SMe$	NHMe
	II-33	$NHCOCH_2$-(1-phthalimido)	$C(Me)_2SMe$	NHMe
15	II-34	$NHCOCH_2$-(1-phthalimido)	$C(Me)_2SMe$	NH(3-pyridylmethyl)
	II-35	1-phthalimido	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-36	1-phthalimido	$C(Me)_2SMe$	NH(3-pyridylmethyl)
	II-37	1-phthalimido	$C(Me)_2SMe$	NHMe
	II-38	1-succinimido	$C(Me)_2SMe$	NHMe
20	II-39	1-succinimido	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-40	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$C(Me)_2SMe$	NHMe
	II-41	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$C(Me)_2SMe$	$NHCH_2CH_2$-morpholino
	II-42	NH_2	$C(Me)_2SMe$	$NHCMe_3$
	II-43	NH_2	$C(Me)_2SMe$	NH-isobutyl
25	II-44	NH_2	$CH(CH_3)OH$	NHMe
	II-45	NH_2	$CH(CH_3)OH$	$NHC(Me)_3$
	II-46	$NHCOOCMe_3$	$CH(CH_3)OH$	NHMe
	II-47	NHCO-morpholino	$CH(CH_3)OH$	$NHC(Me)_3$
	II-48	NH_2	$CH(CH_3)OCMe_3$	NHMe
30	II-49	$NHCOOCMe_3$	$CH(CH_3)OCMe_3$	NHMe
	II-50	NH_2	$CH(CH_3)OCMe_3$	NH(2-thiazolyl)

II-51	NH_2	$CH(CH_3)OCMe_3$	NH(2-pyridyl)
II-52	$NHCOOCMe_3$	$CH(CH_3)OCMe_3$	NH(2-pyridyl)
II-53	NH_2	$CH(CH_3)OCMe_3$	NH(5-indanyl)
II-54	NH_2	$CH(CH_3)OCMe_3$	NH-phenyl
II-55	NH_2	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-56	$NHCOOCMe_3$	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-57	$NHCOOCMe_3$	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-58	$NHSO_2Me$	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-59	$NHSO_2Me$	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-60	$NHSO_2C_6H_4$-*p*-Me	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-61	$NHSO_2C_6H_4$-*p*-Me	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-62	NHCOMe	$CH(CH_3)OCMe_3$	NHMe
II-63	NHCOMe	$CH(CH_3)OCMe_3$	$NHCH_2CH_2NHSO_2$-(morpholino)
II-64	NHCO-morpholino	$CH(CH_3)OCMe_3$	NHMe
II-65	NHCO-morpholino	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-66	NHCO-morpholino	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-67	NHMe	$CH(CH_3)OCMe_3$	NHMe
II-68	NMe_2	$CH(CH_3)OCMe_3$	NHMe
II-69	4-morpholinyl	$CH(CH_3)OCMe_3$	NHMe
II-70	$NHCOCH_2$-(1-phthalimido)	$CH(CH_3)OCMe_3$	NH(3-pyridylmethyl)
II-71	1-phthalimido	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-72	1-phthalimido	$CH(CH_3)OCMe_3$	NHMe
II-73	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$CH(CH_3)OCMe_3$	NHMe
II-74	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$CH(CH_3)OCMe_3$	$NHCH_2CH_2$-morpholino
II-75	NH_2	$CH(CH_3)OCMe_3$	NH-tBu
II-76	NH_2	$CH(CH_3)OCMe_3$	NH-isobutyl
II-77	$NHCH_2CONH_2$	$CH(CH_3)OCMe_3$	NHMe
II-78	$NHCH_2CONMe_2$	$CH(CH_3)OCMe_3$	NHMe
II-79	$NHCH_2CO$-morpholino	$CH(CH_3)OCMe_3$	NHMe
II-80	$NHCOCH_2$-(1-hydantoinyl)	$CH(CH_3)OCMe_3$	NHMe
II-81	$NHCOCH_2$-(3-hydantoinyl)	$CH(CH_3)OCMe_3$	NHMe

II-82	$NHCOCH_2$-(1.5.5-trimethyl-3-hydantoinyl)	$CH(CH_3)OCMe_3$	NHMe
II-83	NHCO-morpholino	CH_2-indolyl	NHMe
II-84	NH_2	CH_2-indolyl	NH-tBu
II-85	NH_2	CH_2-indolyl	NHMe
II-86	$NHCOOCMe_3$	CH_2-indolyl	NHMe
II-87	NH_2	CMe_2Ph	NHMe
II-88	$NHCOOCMe_3$	$CH_2C_6H_4$-*p*-OCH_2COOH	NHMe
II-89	$NHCOOCMe_3$	$CH_2C_6H_4$-*p*-OCH_2COOH	NH-tBu
II-90	$NHCOCMe_3$	$CH_2C_6H_4$-*p*-OCH_2COOH	NH-tBu
II-91	NH_2	$-(CH_2)_{10}$-NH-	
II-92	$NHCOOCMe_3$	$-(CH_2)_{10}$-NH-	
II-93	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$-(CH_2)_{10}$-NH-	
II-94	NHCO-morpholino	$-(CH_2)_{10}$-NH-	
II-95	$NHSO_2$-morpholino	$-(CH_2)_{10}$-NH-	
II-96	$NHCOCH_2$-(1-hydantoinyl)	$-(CH_2)_{10}$-NH-	
II-97	NH_2	$-(CH_2)_4$-NH-$(CH_2)_5$-NH-	
II-98	$NHCOOCMe_3$	$-(CH_2)_4$-NH-$(CH_2)_5$-NH-	
II-99	$NHCOCH_2$-(1-oxo-2-isoindolinyl)	$-(CH_2)_4$-NH-$(CH_2)_5$-NH-	
II-100	$NHCH_2$-C_6H_4-*p*-F	$-(CH_2)_4$-NH-$(CH_2)_5$-NH-	
II-101	$NHSO_2$-C_6H_4-*p*-Me	$-(CH_2)_4$-NH-$(CH_2)_5$-NH-	
II-102	NH_2	$-CH_2$-(3,1-indolylene)-$(CH_2)_6$-NH-	
II-103	NH_2	$-CH_2-C_6H_4$-*p*-O-$(CH_2)_3$-NH-	
II-104	NH_2	$CH_2-C_6H_4$-*p*-OH	NHMe
II-105	$NHCOOCMe_3$	$CH_2-C_6H_4$-*p*-OH	NHMe
II-106	NH_2	CH_2-(1-naphthyl)	NHMe
II-107	NH_2	CH_2-(2-naphthyl)	NHMe
II-108	NH_2	CH_2-(N-methylindolyl)	NHMe
II-109	NH_2	$CH(CH_3)OMe$	NHMe
II-110	NH_2	$CH(CH_3)O$-iPr	NHMe
II-111	NH_2	$CH(CH_3)OPh$	NHMe
II-112	NH_2	4-fluorophenylmethyl	NHMe

II-113	NH_2	4-fluorophenylmethyl	NH-tBu
II-114	NH_2	3-pyridylmethyl	NH-tBu
II-115	NH_2	2-thiazolylmethyl	NH-tBu
II-116	NH_2	cyclohexyl	NHMe
II-117	NH_2	cyclohexyl	NH-tBu
II-118	NH_2	cyclohexyl	NH-$CHPh_2$
II-119	NH_2	7-isoquinolylmethyl	NHMe
II-120	NH_2	7-isoquinolylmethyl	NH-tBu
II-121	NH_2	-$(CH_2)_3OH$	NH-tBu
II-122	NMe_2	tBu	NHMe
II-123	NH-CH_2-C_6H_4-*p*-F	tBu	NH-tBu

Another particularly preferred group of compounds of the present invention encompasses compounds of formula (I') above wherein:

R_2 is a C_7 -C_{15} linear alkyl; or

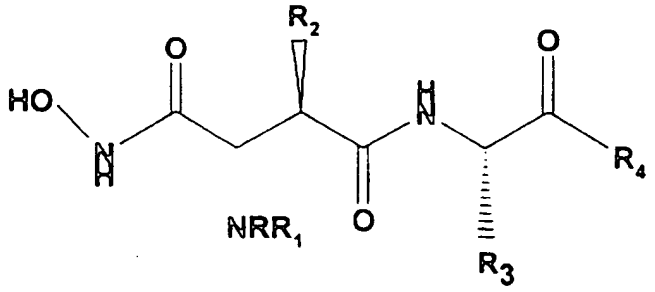
R_2 is cyclopentylmethyl; or

R_2 is cinnamyl, benzyl, (phenyl)ethyl, (phenyl)propyl, (phenyl)butyl, 4-phenyl-3-butenyl, 4-phenyl-3-butinyl, (phenyl)pentyl, (phenoxy)methyl, (phenoxy)ethyl, (phenoxy)propyl, (phenoxy)butyl, (phenoxy)pentyl, (benzylaminocarbonyl)propyl, phenylthio, (phenylthio)methyl, (phenylthio)ethyl, (phenylthio)propyl, phenylsulfonyl, (phenylsulfonyl)methyl, (phenylsulfonyl)ethyl, (phenylsulfonyl)propyl, including derivatives wherein the benzene ring of such groups is substituted, preferably in the para position, by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, hydroxy, methoxy, chloro, fluoro, trifluoromethyl, phenyl, fluorophenyl, methoxyphenyl, methylphenyl, ethylphenyl, propylphenyl, butylphenyl;

and W, R, R_1, R_3 and R_4 are as defined above.

Representative examples within this particularly preferred group of compounds are those listed in Table III herebelow:

Table III.



#	NRR_1	R_2	R_3	R_4
III-1	NH_2	$CH_2CH=CHPh$ (*E*)	tBu	NHMe
III-2	$NHCOOCMe_3$	$CH_2CH_2CH_2Ph$	tBu	NHMe
III-3	NH_2	$CH_2CH_2CH_2Ph$	tBu	NHMe
III-4	$NHCOOCMe_3$	$CH_2CH_2CH_2Ph$	tBu	NH-tBu
III-5	NH_2	$CH_2CH_2CH_2Ph$	tBu	NH-tBu
III-6	NHCO-morpholino	$CH_2CH_2CH_2Ph$	tBu	NHMe
III-7	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NHMe
III-8	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-tBu
III-9	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-$(CH_2)_2$-C_6H_4-*p*-SO_2NH_2
III-10	NMe_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-tBu
III-11	4-morpholino	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-tBu
III-12	1-phthalimido	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NHMe
III-13	1-succinimido	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NHMe
III-14	NH_2	$CH_2CH_2C_6H_4$-*p*-Cl	tBu	NHMe
III-15	NH_2	$CH_2CH_2C_6H_4$-*p*-OMe	tBu	NHMe
III-16	NHCO-morpholino	$CH_2CH_2C_6H_4$-*p*-OMe	tBu	NHMe
III-17	NH_2	$(CH_2)_3$-C_6H_4-*p*-CF_3	tBu	NHMe
III-18	NH_2	$(CH_2)_5$-Ph	tBu	NHMe
III-19	NH_2	$(CH_2)_5$-Ph	tBu	NH-tBu
III-20	NH_2	$(CH_2)_5$-C_6H_4-*p*-F	tBu	NHMe
III-21	NH_2	$(CH_2)_5$-C_6H_4-*p*-F	tBu	NH-tBu
III-22	NH_2	$(CH_2)_5$-OPh	tBu	NHMe
III-23	NH_2	$(CH_2)_5$-O-C_6H_4-*p*-$(CH_2)_2Me$	tBu	NHMe

III-24	NH_2	$(CH_2)_3$-$CONHCH_2Ph$	tBu		NHMe
III-25	NH_2	$(CH_2)_6$ - CH_3	tBu		NHMe
III-26	NH_2	$(CH_2)_6$ - CH_3	tBu		NH-tBu
III-27	NH_2	$(CH_2)_{i4}$ - CH_3	tBu		NHMe
III-28	NH_2	$(CH_2)_3$- C_6H_4-*p*-Cl	tBu		NH-tBu
III-29	NH_2	$(CH_2)_3$-C_6H_4-*p*-F	tBu		NH-tBu
III-30	NH_2	$(CH_2)_3$-C_6H_4-*p*-Me	tBu		NH-tBu
III-31	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_5	tBu		NHMe
III-32	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_5	tBu		NH-tBu
III-33	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	tBu		NHMe
III-34	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	tBu		NH-tBu
III-35	NMe_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	tBu		NH-tBu
III-36	1-pyrrolidinyl	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F		tBu	NH-tBu
III-37	$NHCH_2C_6H_5$-*p*-OMe	$(CH_2)_3$ -C_6H_4-*p*-C_6H_4-F		tBu	NH-Me
III-38	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	tBu		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-39	NH_2	CH_2-cyclopentyl	tBu		NHMe
III-40	NH_2	CH_2-cyclopentyl	tBu		NH-tBu
III-41	NH_2	CH_2-cyclopentyl	tBu		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-42	NH_2	S-C_6H_5-*p*-OMe	tBu		NHMe
III-43	NH_2	S-C_6H_5-*p*-C_6H_5	tBu		NHMe
III-44	NH_2	S-C_6H_5-*p*-C_6H_4-F	tBu		NHMe
III-45	NH_2	CH_2-S-C_6H_5-*p*-OMe	tBu		NHMe
III-46	NH_2	CH_2-S-C_6H_5-*p*-OMe	tBu		NH-tBu
III-47	NH_2	CH_2-CH_2-S-C_6H_5-*p*-OMe	tBu		NHMe
III-48	NH_2	CH_2-S-C_6H_5-*p*-C_6H_5	tBu		NHMe
III-49	NH_2	CH_2-S-C_6H_5-*p*-C_6H_4-F	tBu		NHMe
III-50	NH_2	SO_2-C_6H_5-*p*-OMe	tBu		NHMe
III-51	NH_2	SO_2-C_6H_5-*p*-C_6H_4-F	tBu		NHMe
III-52	NH_2	CH_2-SO_2-C_6H_4-*p*-OMe	tBu		NHMe
III-53	NH_2	CH_2-SO_2-C_6H_4-*p*-OMe	tBu		NH-tBu
III-54	NH_2	CH_2-SO_2-C_6H_4-*p*-C_6H_4-F	tBu		NHMe

III-55	NH_2	CH_2-CH_2-SO_2-C_6H_4-*p*-OMe		tBu	NHMe
III-56	NH_2	CH_2-CH_2-SO_2-C_6H_4-*p*-F		tBu	NHMe
III-57	NH_2	$(CH_2)_6$-CH_3	cyclohexyl		NH-tBu
III-58	NH_2	$(CH_2)_{14}$-CH_3	cyclohexyl		NH-tBu
III-59	NH_2	$(CH_2)_6$-CH_3	cyclohexyl		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-60	NH_2	CH_2-cyclopentyl	cyclohexyl		NH-tBu
III-61	NMe_2	CH_2-cyclopentyl	cyclohexyl		NH-tBu
III-62	NH_2	CH_2-cyclopentyl	cyclohexyl		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-63	NH_2	$(CH_2)_3$-C_6H_4-OMe	cyclohexyl		NH-tBu
III-64	NMe_2	$(CH_2)_3$-C_6H_4-OMe	cyclohexyl		NH-tBu
III-65	NH_2	$(CH_2)_3$-C_6H_4-OMe	cyclohexyl		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-66	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	cyclohexyl		NHMe
III-67	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	cyclohexyl		NH-tBu
III-68	NH_2	SO_2-C_6H_4-*p*-C_6H_4-F	cyclohexyl		NHMe
III-69	NH_2	CH_2-SO_2-C_6H_4-*p*-C_6H_4-F	cyclohexyl		NHMe
III-70	NH_2	$(CH_2)_3$-C_6H_4-OMe	CH_2-cyclohexyl		NHMe
III-71	NH_2	$(CH_2)_3$-C_6H_4-OMe	CH_2-cyclohexyl		NH-tBu
III-72	NH_2	$(CH_2)_3$-C_6H_4-OMe	CH_2-cyclohexyl		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-73	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	CH_2-cyclohexyl		NHMe
III-74	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	CH_2-cyclohexyl		NH-tBu
III-75	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	CH_2-cyclohexyl		$NHCH_2CH_2C_6H_4$-*p*-SO_2NH_2
III-76	NH_2	$(CH_2)_3$-C_6H_4-OMe	$C(Me_2)SMe$		NHMe
III-77	NH_2	$(CH_2)_3$-C_6H_4-OMe	$C(Me_2)SO_2Me$		NHMe
III-78	NH_2	$(CH_2)_3$-C_6H_4-OMe	$(CH_2)_3$-OMe		NHMe
III-79	NH_2	$(CH_2)_3$-C_6H_4-F	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-80	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-F	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-81	NH_2	$(CH_2)_3$-C_6H_4-OMe	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-82	NH_2	CH_2-cyclopentyl	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-83	NH_2	SO_2-C_6H_4-OMe	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-84	NH_2	SO_2-C_6H_4-Ph	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		
III-85	NH_2	CH_2-SO_2-C_6H_4-OMe	-CH_2-(3,1-indolylene)-$(CH_2)_6$-NH-		

III-86	$NHCOOCMe_3$	$CH_2CH_2CH_2Ph$	CH_2Ph	NH-CH_2-CH_2-(4-morpholino)
III-87	$NHCOOCMe_3$	$CH_2CH_2CH_2Ph$	CH_2Ph	NHMe
III-88	NH_2	$CH_2CH_2CH_2Ph$	CH_2Ph	NHMe
III-89	NH_2	CH_2CH_2CH=$CHPh$	tBu	NHMe
III-90	NMe_2	CH_2CH_2CCPh	cyclohexyl	NH-tBu

Still another particularly preferred group of compounds of the present invention encompasses compounds of formula (I') above wherein:

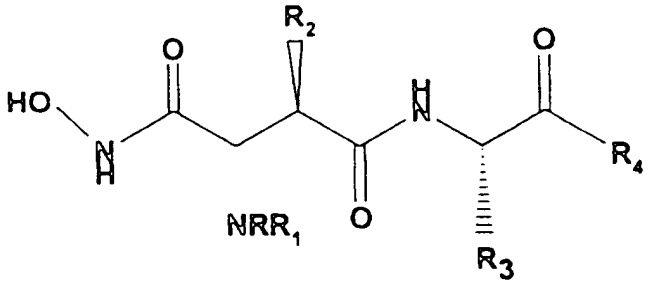
R_4 is either NH-aryl or NH-heterocyclyl, wherein aryl and heterocyclyl are as defined above, either unsubstituted or subsituted by one to three substituents selected from methyl, ethyl, fluoro, chloro and methoxy; or

R_4 is either O-alkyl, wherein alkyl is a C_1 -C_4 straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 -C_4 straight or branched alkyl, chloro and methoxy;

and W, R, R_1, R_2 and R_3 are as defined above.

Representative examples within this particularly preferred group of compounds are those listed in Table IV herebelow:

Table IV.



#	NRR_1	R_2	R_3	R_4
IV-1	NH_2	iBu	CH_2Ph	NH-(4-pyridyl)
IV-2	NH_2	iBu	tBu	NH-(4-pyridyl)
IV-3	NH_2	iBu	cyclohexyl	NH-(4-pyridyl)
IV-4	NH_2	iBu	CH_2-cyclohexyl	NH-(4-pyridyl)

	IV-5	NH_2	CH_2-cyclopentyl	CH_2Ph	NH-(4-pyridyl)
	IV-6	NH_2	CH_2-cyclopentyl	CH_2-C_6H_4-*p*-F	NH-(4-pyridyl)
	IV-7	NH_2	CH_2-cyclopentyl	tBu	NH-(4-pyridyl)
	IV-8	NH_2	CH_2-cyclopentyl	cyclohexyl	NH-(4-pyridyl)
	IV-9	NH_2	CH_2-cyclopentyl	CH_2-cyclohexyl	NH-(4-pyridyl)
	IV-10	NH_2	$(CH_2)_6$-Me	tBu	NH-(4-pyridyl)
	IV-11	NH_2	$(CH_2)_6$-Me	cyclohexyl	NH-(4-pyridyl)
	IV-12	NH_2	$(CH_2)_3$-C_6H_5	tBu	NH-(4-pyridyl)
	IV-13	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-(4-pyridyl)
	IV-14	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	cyclohexyl	NH-(4-pyridyl)
	IV-15	NH_2	$(CH_2)_3$-C_6H_4-*p*-Cl	tBu	NH-(4-pyridyl)
	IV-16	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	tBu	NH-(4-pyridyl)
	IV-17	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	cyclohexyl	NH-(4-pyridyl)
	IV-18	NH_2	iBu	CH_2Ph	NH-(4-F-Ph)
	IV-19	NH_2	iBu	tBu	NH-(4-F-Ph)
	IV-20	NH_2	iBu	cyclohexyl	NH-(4-F-Ph)
	IV-21	NH_2	iBu	CH_2-cyclohexyl	NH-(4-F-Ph)
	IV-22	NH_2	CH_2-cyclopentyl	CH_2Ph	NH-(4-F-Ph)
	IV-23	NH_2	CH_2-cyclopentyl	CH_2-C_6H_4-*p*-F	NH-(4-F-Ph)
	IV-24	NH_2	CH_2-cyclopentyl	tBu	NH-(4-F-Ph)
	IV-25	NH_2	CH_2-cyclopentyl	cyclohexyl	NH-(4-F-Ph)
	IV-26	NH_2	CH_2-cyclopentyl	CH_2-cyclohexyl	NH-(4-F-Ph)
	IV-27	NH_2	$(CH_2)_6$-Me	tBu	NH-(4-F-Ph)
	IV-28	NH_2	$(CH_2)_6$-Me	cyclohexyl	NH-(4-F-Ph)
	IV-29	NH_2	$(CH_2)_3$-C_6H_5	tBu	NH-(4-F-Ph)
	IV-30	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-(4-F-Ph)
	IV-31	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	cyclohexyl	NH-(4-F-Ph)
	IV-32	NH_2	$(CH_2)_3$-C_6H_4-*p*-Cl	tBu	NH-(4-F-Ph)
	IV-33	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	tBu	NH-(4-F-Ph)
	IV-34	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	cyclohexyl	NH-(4-F-Ph)
	IV-35	NH_2	iBu	CH_2Ph	NH-(3,4-methylenedioxyphenyl)

IV-36	NH_2	iBu	tBu	NH-(3,4-methylenedioxyphenyl)
IV-37	NH_2	iBu	cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-38	NH_2	iBu	CH_2-cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-39	NH_2	CH_2-cyclopentyl	CH_2Ph	NH-(3,4-methylenedioxyphenyl)
IV-40	NH_2	CH_2-cyclopentyl	CH_2-C_6H_4-*p*-F	NH-(3,4-methylenedioxyphenyl)
IV-41	NH_2	CH_2-cyclopentyl	tBu	NH-(3,4-methylenedioxyphenyl)
IV-42	NH_2	CH_2-cyclopentyl	cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-43	NH_2	$(CH_2)_6$-Me	tBu	NH-(3,4-methylenedioxyphenyl)
IV-44	NH_2	$(CH_2)_6$-Me	cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-45	NH_2	$(CH_2)_3$-C_6H_5	tBu	NH-(3,4-methylenedioxyphenyl)
IV-46	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-(3,4-methylenedioxyphenyl)
IV-47	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-48	NH_2	$(CH_2)_3$-C_6H_4-*p*-Cl	tBu	NH-(3,4-methylenedioxyphenyl)
IV-49	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	tBu	NH-(3,4-methylenedioxyphenyl)
IV-50	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	cyclohexyl	NH-(3,4-methylenedioxyphenyl)
IV-51	NH_2	iBu	tBu	NH-(2-thiazolyl)
IV-52	NH_2	iBu	cyclohexyl	NH-(2-thiazolyl)
IV-53	NH_2	CH_2-cyclopentyl	tBu	NH-(2-thiazolyl)
IV-54	NH_2	CH_2-cyclopentyl	cyclohexyl	NH-(2-thiazolyl)
IV-55	NH_2	$(CH_2)_6$-Me	tBu	NH-(2-thiazolyl)
IV-56	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-(2-thiazolyl)
IV-57	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	cyclohexyl	NH-(2-thiazolyl)
IV-58	NH_2	$(CH_2)_3$-C_6H_4-*p*-Cl	tBu	NH-(2-thiazolyl)
IV-59	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	tBu	NH-(2-thiazolyl)
IV-60	NH_2	$(CH_2)_3$-C_6H_4-*p*-C_6H_4-*p*-F	cyclohexyl	NH-(2-thiazolyl)
IV-61	NH_2	CH_2-cyclopentyl	tBu	NH-(5-Me-1,3,4-thiadiazol-2-yl)
IV-62	NH_2	CH_2-cyclopentyl	cyclohexyl	NH-(2-thienyl)
IV-63	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	NH-(2-furyl)
IV-64	$NHCOOCMe_3$	iBu	tBu	O-Me
IV-65	NH_2	iBu	tBu	O-Me
IV-66	NH_2	CH_2-cyclopentyl	tBu	O-tBu

IV-67	NH_2	CH_2-cyclopentyl	cyclohexyl	O-tBu
IV-68	NH_2	CH_2-cyclopentyl	cyclohexyl	O-(2,4,6-trimethylphenyl)
IV-69	NH_2	$(CH_2)_3$-C_6H_4-*p*-OMe	tBu	O-tBu
IV-70	NH_2	CH_2-cyclopentyl	7-isoquinolylmethyl	NH-(2,3-methylenedioxy)phenyl
IV-71	NH_2	CH_2-cyclopentyl	$-(CH_2)_3OH$	NH-(2,3-methylenedioxy)phenyl

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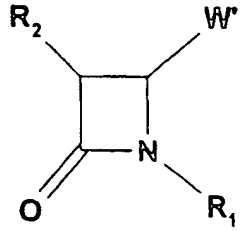
Compounds of the general formula (I) may be prepared by any suitable method known in the art, and/or by the following process, which forms another aspect of the invention. In the description and formulae below, the groups W, R, R_1, R_2, R_3 and R_4 are as defined above. It is understood that in the processes below any functional group (e.g. carboxyl, hydroxyl or amino), if needed or desired, can be masked by conventional methods and unmasked at the end or when convenient. Suitable protecting groups for such functionalities will be apparent to those skilled on the art and are well described in the chemical literature (see, for example: "Protective Groups in Organic Synthesis" by T.W. Greene, Wiley Interscience). It is also understood that any of the groups W, R, R_1, R_2, R_3 and R_4 can be converted by conventional methods into different groups W, R, R_1, R_2, R_3 and R_4 having any of the significance previously defined, if desired, at the end or at any stage of the processes below. These conversions are known or will be apparent to those skilled in the art and are well described in the chemical literature (see, for example: "Comprehensive Organic Transformation" by R.C. Larock, VCH Publishers).

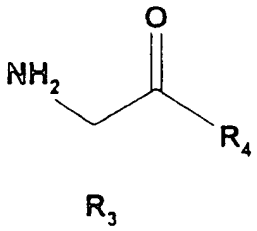
A process for preparing a compound of formula (I) as above defined comprises:

(a) reacting a beta-lactam compound of general formula (II):



(II)

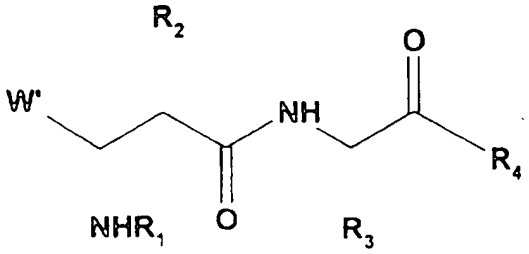
wherein R_1 and R_2 are as defined above, and W' is either COOH, CONHOH or protected derivatives of the same, with an amine of formula (III):



(III)

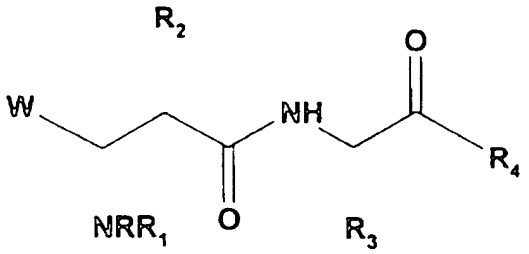
wherein R_3 and R_4 are as defined above; and

b) converting the so-obtained compound of formula (IV):



(IV)

wherein W', R_1, R_2, R_3 and R_4 are as defined above, into a compound of formula (I):

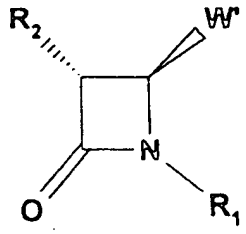


(I)

wherein W, R, R_1, R_2, R_3 and R_4 are as defined above.

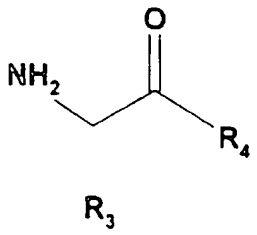
It is evident that compounds with a desired configuration may be prepared starting from compounds (II) and (III) with the appropriate configurations. Thus, a process for preparing preferred compounds of formula (I') comprises:

(a) reacting a beta-lactam compound of general formula (II'):



(II')

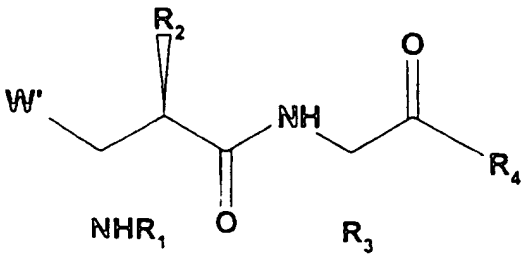
wherein R_1 and R_2 are as defined above, and W' is either COOH, CONHOH or protected derivatives of the same, with an amine of formula (III'):



(III')

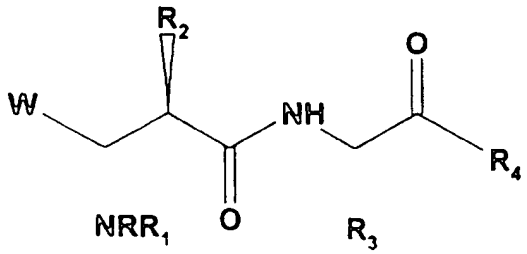
wherein R_3 and R_4 are as defined above: and

b) converting the so-obtained compound of formula (IV'):



(IV')

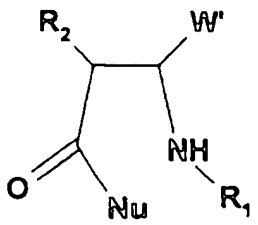
wherein W', R_1, R_2, R_3 and R_4 are as defined above, into a compound of formula (I'):



(I')

wherein W, R, R_1, R_2, R_3 and R_4 are as defined above.

The reaction between the beta-lactam of formula (II) and the amine of formula (III) in step (a) above can be carried out in organic solvents, especially dimethylformamide (hereinafter DMF), tetrahydrofuran (hereinafter THF), acetonitrile, and toluene, or in aqueous organic solvents, especially aqueous THF, aqueous DMF, and aqueous acetonitrile, at temperatures ranging from 0 to 120 °C, either in the absence or in the presence of external bases, or of nucleophiles (NuH or salts thereof, wherein Nu is herebelow defined) which cleave the beta-lactam of formula (II) more readily than the amine of formula (III), giving rise to activated carboxylic acid derivatives of formula (IIa):



(IIa)

wherein W', R_1 and R_2 are as defined above, and Nu is selected from the group consisting of azido, imidazole, cyano, lower alkylthio, pyridylthio, phenylthio, and benzylthio; said activated carboxylic acid derivative of formula (IIa) reacting, in the same milieu and under the same reaction conditions, with the amine of formula (III), giving rise to the product of formula (IV). Particularly preferred external nucleophiles are sodium azide, imidazole, and sodium and potassium cyanide. A particularly preferred solvent is DMF. When in compounds of formula (II), (IIa) and (IV) above W' is a protected derivative of COOH, it is preferably benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-methoxybenzyl oxycarbonyl, tert-butoxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, trimethylsilyloxycarbonyl, tert-butyldimethylsilyloxycarbonyl, phenyl-dimethylsilyloxycarbonyl, allyloxycarbonyl, methoxycarbonyl and ethoxycarbonyl. When in compounds of formula (II), (IIa) and (IV) above W' is a protected derivative of CONHOH, it is preferably a group of formula $CONHOR_{10}$ or $CON(R_{11})OR_{10}$, wherein R_{10} and R_{11} are, respectively, hydroxy- and amino-protecting groups, known per se and removable by hydrogenolysis or by hydrolysis. Preferred R_{10} and R_{11} groups, which may be the same or different, include benzyl, p-methoxybenzyl, p-nitrobenzyl, trimethylsilyl, tert-butoxycarbonyl, tetrahydropyranyl, and trityl. The conversion of a compound of formula (IV) into a compound of formula (I) in step (b) above may include any or all of the following steps in any order:

-(b'): the conversion of the group W', which is a protected derivative of W, into a group W, which is either COOH or CONHOH. This conversion is carried out by methodologies well known in the art, as generally referred to above. A preferred conversion of this type is hydrogenolysis, especially in the presence of a palladium catalyst, in an inert organic solvent such as ethanol or DMF or the like, especially at room temperature and under atmospheric pressure or moderate pressure, which is suitable for the conversion, e.g., of benzyl and p-nitrobenzyl esters into the parent carboxylic acids, or of O-benzyl and O,N-bis-benzyl hydroxamates into the parent hydroxamic acids. Another preferred conversion of this type is acid hydrolysis, especially by trifluoroacetic acid or by aluminium trichloride, in the presence or absence of anisole, in inert organic solvents such as THF, acetonitrile and the like, especially between -20 and +30 °C, which is suitable for the conversion, e.g., of tert-butyl esters and p-methoxybenzyl esters into the parent carboxylic acids, or of O-(p-methoxybenzyl) and O,N-bis(p-methoxybenzyl) hydroxamates into the

parent hydroxamic acids;

-(b''): the conversion of the group W', which is COOH or an activated derivative thereof, into a group W, which is CONHOH. This conversion entails the condensation of such compounds of formula (IV) with hydroxylamine or a salt thereof, or with an O-protected hydroxylamine of formula $R_{10}O\text{-}NH_2$, or an N,O-diprotected hydroxylamine of formula $R_{10}O\text{-}NHR_{11}$, wherein R_{10} and R_{11} are as defined above, or a salt thereof, and then removal of said protecting groups R_{10} and R_{11} , if present. Such condensation is carried out according to general methodologies for the conversion of carboxylic acids or activated derivatives thereof into hydroxamic acids, which are well known in the art. In particular, activated derivatives of the COOH group are the acid chloride, mixed anhydrides, and esters. In particular, the acid chloride is obtained by reacting the acid or a salt thereof with reagents such as oxalyl chloride or thionyl chloride; mixed anhydrides are obtained by reacting the acid or a salt thereof with chlorocarbonates, such as ethyl chlorocarbonate, or with acid halides, such as pivaloyl chloride; ester, which are, preferably, the methyl, ethyl, pentafluorophenyl, hydroxysuccinyl, or hydroxybenzotriazolyl esters, are obtained by reaction of the acid with the corresponding alcohols in the presence of a dehydrating agent, for example dicyclohexyl carbodiimide (hereinafter DCC), N,N-dimethylaminopropyl-N'-ethyl carbodiimide (EDC), and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ). An O-protected hydroxylamine is, preferably, O-benzyl-hydroxylamine, O-(4-methoxybenzyl)-hydroxylamine, O-trimethylsilyl-hydroxylamine, and O-(tert-butoxycarbonyl)-hydroxylamine. An N,O-diprotected hydroxylamine is, preferably, N,O-bis(benzyl)-hydroxylamine, N,O-bis(4-methoxybenzyl)-hydroxylamine, N,O-bis(tert-butoxycarbonyl)-hydroxylamine, N-(tert-butoxycarbonyl)-O-(tert-butyldimethylsilyl)-hydroxylamine, and N-(tert-butoxycarbonyl)-O-(tetrahydropyranyl)-hydroxylamine. Preferably, the condensation reaction with hydroxylamine, O-protected hydroxylamines, N,O-diprotected hydroxylamines, and the salts thereof, is carried out in an inert organic solvent, such as DMF, THF, acetonitrile, dichloromethane, toluene and the like, at temperatures ranging from -20 to + 60 °C, optionally in the presence of a tertiary organic base. When protected hydroxylamines are employed, the protecting groups are removed after the condensation reaction, under the conditions well known per se. For example, benzyl and 4-methoxybenzyl groups may be removed, preferably, by catalytic hydrogenation, as described in step (b') above; tetrahydropyranyl and tert-butoxycarbonyl

groups may be removed, preferably, by mild acid hydrolysis; trimethylsilyl and tert-butyldimethylsilyl groups are cleaved off during the reaction or by aqueous workup or by mild acid treatment;

-(b^{iii}): the conversion of the group NHR_1, being R_1 different from hydrogen, into a group NH_2. This reaction can be carried out on compounds of formula (I) or intermediates of formula (IV) wherein R_1 is an amino protecting group, according to methods well known per se, for example by the methods of removal of amino protecting groups which are part of the techniques of peptide chemistry. Particularly preferred R_1 groups for such conversion are electron-withdrawing groups, in particular alkoxy- or benzyloxy-carbonyl groups such as tert-butoxycarbonyl, benzyloxycarbonyl and 4-nitro or 4-methoxy derivatives thereof, since the same particular R_1 groups efficiently assist the beta-lactam cleavage reaction between a compound of formula (II) and a compound of formula (III), as defined above, to give a compound of formula (IV). In a preferred embodiment of the present invention, R_1 is tert-butoxycarbonyl, which can be removed by treatment with trifluoroacetic acid (TFA), optionally in the presence of anisole, in an inert organic solvent; in another preferred embodiment, R_1 is benzyloxycarbonyl or 4-nitrobenzyloxycarbonyl, which can be removed by catalytic hydrogenation;

-(b^{iv}): the conversion of the group NHR_1, including the special case wherein R_1 is hydrogen, into a group NRR_1, to be selected within the specifications stated above. Preferred R and R_1 groups are the same groups detailed for the preferred compounds of formula (I). Such conversion encompasses functionalizations of amino groups well known in the art, such as alkylation, acylation, sulfonylation, and the like, and is performed according to methods well known per se. In a preferred embodiment of the present invention, such conversion is performed on compounds of formula (IV) wherein W' is protected carboxy, thereafter removing the protecting group to obtain a compound of formula (I) wherein W is COOH by the general methodology described under (b') above and, optionally, by converting the so-obtained compound of formula (I) wherein W is COOH into the corresponding compound wherein W is CONHOH by the general methodology described under (b") above;

-(b^{v}): the conversion of any group R, R_1, R_2, R_3 and R_4 into any different group R_1, R_2, R_3 and R_4, to be selected within the specifications stated above, by methodologies known per se.

The resultant compounds of formula (I) may be converted into the desired salts, prodrugs, hydrates or solvates thereof by means of well known reactions, which include salts preparation by reaction with a pharmaceutically acceptable acid, or esters preparation by condensation with a pharmaceutically acceptable alcohol or with a pharmaceutically acceptable carboxylic acid, and mixing with an aldehyde of general formula T-CHO or a ketone of general formula TT'CO, wherein T and T' are as defined above, and removing water by evaporation.

The amines of formula (III) above are known compounds or are prepared from known compounds by known methods.

The beta-lactams of formula (II) above are known compounds or can be prepared from known compounds by methodologies known per se or by analogy with the specific preparative examples herein. In particular, a preferred preparation of compounds of formula (II) includes:

-(i): cyclization of an aspartic acid derivative to obtain a compound of formula (II) wherein R_2 is hydrogen, by reaction with a suitable condensing agent;

-(ii): conversion of a compound of formula (II) wherein R_2 is hydrogen into a compound of formula (II) wherein R_2 is as described above, by deprotonation with a strong base and alkylation of the resulting beta-lactam enolate with an agent of formula R_2-X, wherein X is halo, e.g. chloro, bromo or iodo, or sulfonyloxy, e.g. triflate, mesylate or the like.

General conditions for step (i) above are described in the literature, the preferred aspartic acid derivative being usually dibenzyl aspartate or di(4-nitro)benzyl aspartate. Some of the resultant azetidinones (II) are also commercially available. A preferred compound in step (ii) is a compound of formula (II) wherein R_2 is hydrogen, R_1 is tert-butyldimethylsilyl, and W is COOH; such compound is obtained from the product of step (i) wherein R_1 is hydrogen and W is benzyloxycarbonyl or 4-nitrobenzyloxycarbonyl by conventional methods, in particular by catalytic hydrogenolysis and silylation by tert-butyldimethyl chlorosilane.

It is evident that the conditions above described for the reaction of a beta-lactam of formula (II) and an amine of formula (III), for the conversion of a compound of formula (IV) into a compound of formula (I), and for the conversion of the resultant compounds of formula (I) into salts, prodrugs or solvates thereof, also apply for the preferred chiral analogues, that is, respectively, for the reaction of a beta-lactam of formula (II') and an

amine of formula (III'), for the conversion of a compound of formula (IV') into a compound of formula (I'), and for the conversion of the resultant compounds of formula (I') into salts, prodrugs or solvates thereof, since such conditions do not cause epimerization or racemization. Similarly, the conditions above described for the preparation of beta-lactams of formula (II) also apply for the preparation of the preferred chiral analogues of formula (II'), when the aspartic acid derivative in step (i) above is an L-aspartic acid derivative. In fact, in step (i), which involves intramolecular condensation of the ω carboxy group of the aspartic derivative or a derivative thereof, i.e. an acid halide, ester or anhydride, with the α amino group of the same, or a trimethylsilyl derivative thereof, the chirality of the carbon atom is preserved. In step (ii), said chirality induces the configuration of the adjacent stereocenter, i.e. that of the of carbon atom bearing the R_2 group. As it is well known in azetidinone chemistry, alkylation of 3-unsubstituted, 4-substituted azetidinones gives products wherein the C-3 and C-4 substituents are in a transoid relationship to each other. Thus, azetidinones of formula (II') wherein R_2 is a hydrogen atom, which are obtained from L-aspartic acid derivatives, undergo alkylation with reagents of formula R_2-X above to provide azetidinones (II') with the depicted configurations at the two chiral centers. Said configurations of the two chiral centers are the same as found in compounds of formula (I') herein specifically preferred. Accordingly, it can be appreciated that steps (i) and (ii) above are essential part of an original, fully stereocontrolled route to the compounds of formula (I'), which are characterised by the (*S*) and (*R*) configuration, according to the Cahn-Ingold-Prelog rule, at the carbon atoms bearing the NRR_1 and R_2 groups, respectively.

The compounds of formula (I) provided by the present invention are characterized by high inhibitory activity on matrix metalloproteinases (MMPs), especially collagenases, gelatinases and stromelysins. For example, the following protocol was used to assess the biochemical activity of compounds of formula (I) against MMP-1, MMP-2, and MMP-3 (respectively, human interstitial collagenase, gelatinase A, and stromelysin-1).

BIOCHEMICAL ASSAY (Protocol A)

The *in vitro* potency of the compounds of the present invention as competitive inhibitors of selected matrix metalloproteinases was determined as described below.

Human collagenase (MMP-1) was obtained as truncated recombinant enzyme encompassing residues 101-269 and did not required activation. Human gelatinase-A (MMP-2) was obtained as pro-enzyme (72 kDa) and was activated with 1 mM 4-aminophenylmercuric acetate for 30 min at 37 °C immediately prior to use. Human stromelysin-1 1-255 (MMP-3) was obtained as a recombinant pro-enzyme isolated from *E. coli* and activated by heat (1 h. 55 °C). Some measurements were also carried out using a recombinant human MMP-3 pro-enzyme isolated from *baculovirus* infected Sf9 insect cells and activated by 5 mg/l trypsin (30 min. 37°C. finally removed by agarose-soybean trypsin inhibitor).

All enzyme assays to determine the values of the enzyme-inhibitor dissociation constants were performed using the peptide substrate (7-methoxycoumarin-4-yl)Acetyl-Pro-Leu-Gly-Leu-(3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl)-Ala-Arg-NH_2 (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2) [C.G. Knight, F. Willenbrock and G. Murphy. *FEBS Lett.* (1992) 296, 263-266]. The enzymes cleave at the Gly-Leu bond removing the internally quenching Dpa group. The release of the highly fluorescent peptide Mca-Pro-Leu was followed fluorimetrically using a Perkin Elmer LS-50 Fluorescence Spectrophotometer fitted with a thermostatted four position stirring cell changer. The excitation wavelength was set at 326 nm (bandwidth 5 nm) and the emission at 392 nm (bandwidth 20 nm). All other setting was optimised for the best signal/noise ratio. All experiments were carried out at 37°C.

Substrate concentration was 2 micromolar in the tests, so that we could approximate to unit the term (1 + [substrate] / Km) in calculations, being Km values 70 micromolar or greater for the three MMP's (Knight, Willenbrock and Murphy). The substrate was stable for over 60 minutes in the assay conditions, giving no appreciable increment of fluorescence. Full response was adjusted against 200 nM Mca-Pro-Leu-OH (the released fluorescent peptide) and the instrument was calibrated in the range 0-100 nM Mca-Pro-Leu-OH, corresponding to 0-5% extent of hydrolysis of the 2 micromolar substrate.

The aqueous assay buffer was 50 mM Tris/HCl pH=7.4 containing 0.15 M NaCl, 10 mM CaCl2, 0.01 mM ZnCl2 and 0.05% Brij 35. Inhibitors were generally dissolved in DMSO and added at 1:100 ratio. The same was for substrate, so that the actual DMSO concentration in the tests was kept at 2% (v/v).

Enzyme concentrations in the tests were generally 1.0 nM collagenase, 0.04 nM gelatinase-A and 3.0 nM stromelysin. Under our assay conditions we measured k cat / Km values of 26900, 669000 and 9740 1/(M×s) for MMP-1, MMP-2 and MMP-3, respectively. All the three enzymes were found stable for over three hours in the assay conditions.

Preliminary investigations were carried out on some representative inhibitors by continuous fluorescence. In detail, 1.94 ml of assay buffer was pre-heated at 37°C and added of 0.02 ml inhibitor in DMSO (or DMSO only), 0.02 ml of 0.2 mM substrate, and 0.02 ml of 100 nM MMP1 or 4 nM MMP2 or 300 nM MMP3. The increase in fluorescence was generally monitored over 30 min. The enzymes were found stable over a 30 min pre-incubation time period in the same conditions. Inhibitors concentrations ranged 0.01 - 50000 nM, depending on enzyme and potency. The extent of substrate hydrolysis was well within 5% of the total concentration.

Such representative inhibitors were found to be reversible competitive inhibitors and the simplest competive slow-tight binding inhibition model which accounted for observations was a two-steps mechanism E + I <=> EI <=> EI* where the rate-determining step is conversion of the initial enzyme-inhibitor complex EI into the more stable one EI*. We could obtain dissociation and rate constants of the enzyme-inhibitor complexes by analysis of progress curve data for slow, tight-binding inhibition as described by Morrison and Walsh [J.F. Morrison and C.T. Walsh, *Adv. Enzymol. Relat. Areas Mol. Biol.* (1988) 61, 201-301].

Moreover, with the aim to screen quickly large numbers of inhibitors, we also focussed experiments to determine just the overall dissociation constant Ki* = [E]free x [I]free / [EI + EI*] (Morrison and Walsh), that is the Ki measured at stady state, upon preincubation experiments. All concentrations and conditions were the same as above, but in this case we just measured Vo, the initial rate in the absence of inhibitor, and Vs,the staedy-state velocity, at different concentrations of inhibitors in the region if their enzyme-inhibitor dissociation constants.

On a routine basis 1.94 ml of assay buffer was pre-heated at 37°C in a vial, 0.02 ml of inhibitor in DMSO (or DMSO only), and 0.02 ml of 100 nM MMP-1 or 4 nM MMP-2 or 300 nM MMP-3 were added, mixed, and the vial was held at 37°C for 5-180 minutes. Then 0.02 ml of 0.2 mM substrate was added, mixed and transferred into a pre-heated cell. The sample was allowed to equilibrate in the cuvette for 3-5 min at 37°C against small changes in temperature and changes in the enzyme-inhibitor equilibria related to addition of substrate. After that the linear increase of fluorescence was monitored over 3-5 min and the slope (Vo or Vs) was obtained.

Inhibitor concentrations were varied to collect data over Vs/Vo ratio ranging 0.05-0.95. The values of Ki* were calculated by nonlinear weighted regression to the tight-binding equation (Morrison and Walsh):

$$Vs/Vo=[1/(2 \times Et)] \times SQR[(Ki^* + It - Et)^2 + 4 \times Ki^* \times Et] - (Ki^* + It - Et)$$

being Et and It the total enzyme and inhibitor concentrations.

Lowest limits of determination of Ki* were dictated by enzyme concentrations: even if regression to the tight-binding equation takes into account Et, which was known by preliminary titration, generally we could not obtain reliable estimation of Ki* values lower than 1/2 - 1/4 of Et. In our case this means about 200-500 pM Ki* with collagenase, 10-20 pM Ki* with gelatinase-A or 0.8-1.5 nM Ki* with stromelysin.

By definition, measurements must be carried out under "steady-state" conditions. When Ki* is very low, approaching Et, and It is varied in the region of its Ki* value, than the establishment of the equilibria between enzyme, inhibitor and enzyme-inhibitor complexes may take more than few minutes to occur (Morrison and Walsh). For this reason the experiments were repeated extending the pre-incubation time of enzyme and inhibitor (5 min by default) up to three hours all times we measured Ki* values in the low nanomolar range or less. However, with the inhibitors of the present invention to date examined we rarely found any difference extending the pre-incubation time from 5 minutes to three hours or more, even with inhibitors showing very low values of Ki*.

As an example, Table V reports the inhibition constants, Ki at steady state, as determined by the above protocol (A) for 14 compounds of the present invention.

TABLE V. INHIBITION CONSTANTS (Ki at steady state, all nanomolar)

EXAMPLE#	COMPOUND	MMP-1	MMP-2	MMP-3
2	I-25	3.6	1.6	5.0
4	I-2	0.8	1.7	5.4
6	I-44	1.1	10	9.5
8	I-61	0.7	1.2	31
10	I-72	1.6	6.6	14
12	IV-64	140	85	450
13	IV-65	14	57	930
16	III-87	38	0.16	2.3
17	III-88	7.8	0.012	1.1
18	I-21	1.2	1.3	16
20	II-122	1.9	10	11
21	IV-2	0.6	1.1	1.7
22	IV-41	< 0.2	0.6	0.5
23	II-102	0.5	1.3	3.9

The compounds of formula (I) were also shown to possess high activity at inhibiting the release of TNF of several different cell lines, under different stimulation conditions. For example, the following cell-based assay was used to assess such activity:

CELLULAR ASSAY (Protocol B)

The *in vitro* potency of the compounds of the present invention as inhibitors of the release of TNF from cells was determined as described below. THP-1 cells, cultured in RPMI 1640 supplemented with 10% FCS, were distributed into 24-well plates, 1 mL of a suspension of $1x10^6$ cells/mL in each well. Compounds to be tested, dissolved in DMSO and diluted with the culture medium (1% final DMSO concentration) were added. Plates were incubated for 30 min at 37 °C in 5% CO_2 , and lipopolisaccharide (LPS 0111:B4, 5 microg/mL) was added as a stimulant. After a further 4 h incubation, cells were harvested, centrifuged (2,000 rpm, 7 min), and the sumatant was collected and freezed (-20 °C) until analysis. Analysis was run by classical ELISA methodology (monoclonal anti-TNF-α antibody, rabbit capture policlonal antibody, and peroxidated anti-rabbit antibody). Dichloroisocoumarin was used as a standard.

As an example, Table VI reports the IC_{50} values (all micromolar), as determined by the above protocol (B) for 7 compounds of the present invention.

TABLE VI. INHIBITION OF TNF-alpha RELEASE FROM THP-1 CELLS

EXAMPLE #	COMPOUND	IC_{50} (μM)
2	I-25	9.9
6	I-44	1.2
8	I-61	25.1
12	IV-64	40.5
13	IV-65	127.8
16	III-87	12.8
17	III-88	1.9

The amino or substituted-amino functionality alpha to the carboxy or hydroxamic function, which characterizes the compounds of the present invention, not only contributes to improve biochemical potency, but in many cases also contributes to improving aqueous solubility and pharmacokinetic properties.

Poor aqueous solubility is a major limitation of the most potent hydroxamate-based MMP inhibitors of the prior art. Compounds of formula (I) wherein the group $-NRR_1$ is a primary, secondary or tertiary amino group exist in the protonated form at physiological pH; consequently, their aqueous solubility is high (> 5 mM) or moderate (> 1 mM), even when one or more of the groups R, R_1 -R_4 is of highly lipophilic nature. This feature contributes to improving absorption through the gastrointestinal wall. As an example, Table VII reports the solubility of 12 compounds of the present invention in physiological saline at 25 °C.

TABLE VII. SOLUBILITY IN SALINE, 25 °C

EXAMPLE#	COMPOUND	Soluble at (mg/mL):
4	I-2	> 7
6	I-44	0.05
10	I-72	0.03
12	IV-64	0.25
13	IV-65	> 9

16	III-87	0.01
17	III-88	2.4
18	I-21	> 8
20	II-122	> 5
21	IV-2	> 13
22	IV-41	> 10
23	II-102	0.5

Compounds of formula (I), therefore, can be used in human or veterinary medicine in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier material. Thus, a distinct aspect of the present invention is the preparation of pharmaceutical compositions carrying a compound of formula (I) as active ingredient, and a method of management (i.e. treatment or prophylaxis) of diseases or conditions mediated in humans and warm blood animals by MMPs and/or TACE, which method comprises administering to the mammal an effective amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof, to humans and animals.

In particular, the compounds of formula (I) can be administered:

A) Orally, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal

tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy propylmethylcellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin. Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring

agents. may also be present. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil. for example olive oil or arachis oils. or a mineral oil. for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums. for example gum acacia or gum tragacanth. naturally-occurring phosphatides, for example soy bean, lecithin. and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate. and condensation products of the said partial esters with ethylene oxidc. for example polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents. for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent. a preservative and flavoring and coloring agents:

B) Parenterally. either subcutaneously. or intravenously, or intramuscularly, or intrasternally, or by infusion techniques. in the form of sterile injectable aqueous or oleaginous suspensions. This suspension may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1.3-butane diol. Among the acceptable vehicles and solvents that may be employed are water. Ringer's solution and isotonic sodium chloride solution. In addition. sterile. fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables;

C) By inhalation. in the form of aerosols or solutions for nebulizers;

D) Rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols;

E) Topically, in the form of creams ointments, jellies. solutions or suspensions.

Daily doses are in the range of about 0.1 to about 50 mg per kg of body weight. according to the activity of the specific compound. the age, weight and conditions of the subject to be treated. the type and severity of the disease, and the frequency and route of

administration; preferably, daily dosage levels for humans are in the range of 10 mg to 2 g. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans, may contain from 5 mg to 2 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient.

Pharmaceutical compositions containing a compound of formula (I) can be used in medicine for the treatment of disease states characterised by an imbalance of active MMPs and their natural inhibitors, the tissue inhibitors of metalloproteinases (hereinafter TIMPs). When local TIMP levels are insufficient, or MMPs are over-expressed or over-activated from their secreted inactive zymogens (pro-MMPs), degradation of the extracellular matrix occurs. This degradation can be slow and progressing, as observed, for example, for cartilage matrix loss in rheumatoid arthritis (L.A. Walakovits et al., Arthritis Rheum. 35:35-42, 1992) and osteoarthritis (D.D. Dean et al., J. Clin. Invest., 84:678-685, 1989), and for bone matrix degradation in osteoporosis (P.A. Hill et al., Biochem. J., 308:167-175, 1995). In other situations, such as congestive heart failure, rapid degradation of the heart's extracellular matrix occurs (P.W. Armstrong et al., Canadian J. Cardiol. 10:214-220, 1994). Cancer cells use MMPs, either expressed by themselves or by the surrounding tissues, to achieve rapid remodelling of the extracellular matrix. There is considerable evidence that MMPs are involved in at least 3 aspects of the growth and spread of tumors (e.g., see A.H. Davidson et al., Chemistry & Industry, 258-261, 1997, and references therein). In the process of tumor metastasis, MMPs are used to break down the extracellular matrix, allowing primary tumor cancer cells to invade neighbouring blood vessels where they are transported to different organs and establish secondary tumors. The invasive growth at these secondary sites also needs MMPs to help break down tissue. In addition, MMP activity contributes to the invasive in-growth of new blood vessels (angiogenesis) which is required for tumors to grow above a certain size.

The rationale for the use of MMP inhibitors in medicine is well described in the recent literature; see, for example, D.E. Levy & A.M. Ezrin, "Matrix Metalloproteinase Inhibitor Drugs", in: Emerging Drugs: The Prospect for Improved Medicines, Chapter Ten (pp 205-

230), Ashley Publications Ltd., 1997. According to this rationale, and proofs of concept already established with other MMP inhibitors, the compounds of the present invention can be used, in particular, for the treatment of:

- inflammatory and autoimmune diseases, especially rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal disease, and multiple sclerosis;
- cancer, including both tumor growth and metastasis, with particular reference to breast cancer, small cell lung cancer, non-small cell lung cancer, brain tumors, prostate cancer, colorectal tumors and Kaposi's sarcoma;
- other angiogenic disorders, especially diabetic retinopathies and macular diseases;
- cardiovascular diseases, especially congestive hearth failure and vascular restenosis;
- wound healing, including ocular inflammation, corneal or tissue ulceration, soft and osseous tissue diseases;
- other disorders in which either MMPs or release of TNF-alfa is implicated, in particular psoriasis, shock syndromes and transplant rejection.

The present invention also includes the use of compounds of formula (I), for the treatment of any of the diseases above, as adjuncts to other conventional treatments; for example, together with anti-inflammatory or immunosuppressive drugs for the treatment of rheumatoid arthritis and multiple sclerosis, and together with cytotoxic or cytostatic drugs for the treatment of tumoral diseases.

EXAMPLE 1

(3S-tert-Butoxycarbonylamino-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-24).

-Step (a): A solution of 1-tert-butyldimethylsilyl-4S-carboxyazetidinone (6.2 g) in dry THF (100 ml) was treated dropwise at 0-5 °C with a 2M solution of LDA (28.4 ml) in the same solvent, to obtain an orange solution of the di-anion. After 15 min, a solution of isobutyl iodide (6.8 ml) in THF was added at 0 °C under stirring, and the resulting green solution was left at the same temperature overnight. Quenching with 1M aqueous $KHSO_4$ (300 ml), followed by extraction with EtOAc, afforded crude 1-tert-butyldimethylsilyl-4S-carboxy-3R-isobutylazetidinone as an orange syrup (7 g).

The above material was dissolved in dry DMF (20 ml) and treated dropwise, in this order, with triethylamine (5.85 ml) and benzyl bromide (4.8 ml). After 4 hr at room temperature,

the mixture was partitioned between water and EtOAc. The organic phase, after washing with saturated aqueous NaCl, was dried and evaporated to obtain crude 4S-benzyloxycarbonyl-1-tert-butyldimethylsilyl-3R-isobutylazetidinone as an orange oil, which was dissolved in THF (10 ml) and left overnight in the presence of tetrabutylammonium fluoride (2.6 g) and acetic acid (1.7 ml). The mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and the organic phase was dried and evaporated. Flash chromatography over silica gel (n-hexane/EtOAc) afforded 4S-benzyloxycarbonyl-3R-isobutyl azetidinone (4.7 g) as white needles. FT-IR (KBr) 3229 (NH), 1744-1750 br (CO) cm^{-1}. NMR (200 MHz, $CDCl_3$) 0.94 (d, 3 H, J= 6.5), 0.87 (d, 3 H, J= 6.5), 1.57-1.82 (m, 3 H), 3.32 (m, 1 H), 3.90 (d, 1 H, J= 2.4), 5.22 (Abq, 2 H), 5.96 (br s, 1 H), 7.36 (m, 5 H) ppm.

-Step (b): A solution of 4S-benzyloxycarbonyl-3R-isobutylazetidinone (1 g) from step (a) above in MeCN (15 ml) was treated with DMAP (4-dimethylaminopyridine; 46 mg) and BOC_2O (di-tert-butyl dicarbonate; 1.67 g) at 40 °C for 30 min and then at room temperature overnight. After removal of the solvent in vacuo, the residue was dissolved in EtOAc and sequentially washed with aqueous 1M $KHSO_4$, saturated $NaHCO_3$, and brine. Drying over Na_2SO_4 and evaporation left crude 4S-benzyloxycarbonyl-1-tert-butoxycarbonyl-3R-isobutylazetidinone (0.83 g) as a yellow oil. FT-IR ($CHCl_3$) 1820 (azetidinone CO), 1750 (ester CO), 1728 (carbamate CO) cm^{-1}.

-Step (c): 4S-Benzyloxycarbonyl-1-tert-butoxycarbonyl-3R-isobutylazetidinone from step (b) above (145 mg) was dissolved in dry DMF (4 ml). To this solution, L-phenylalanine-N-methylamide (p-toluenesulfonate salt; 280 mg), N-methylmorpholine (0.1 ml), and sodium azide (25 mg) were sequentially added. After overnight stirring at room temperature, the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with water and brine. Drying over Na_2SO_4, evaporation and flash chromatography over silica afforded (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide as a white powder (150 mg). FT-IR (KBr) 3312 br (NH), 1735-1695 br and 1647 (CO) cm^{-1}. FAB-MS 484 $(MH)^+$, 384 $(MH\text{-}BOC)^+$, 120, 91 m/z.

-Step (d): A mixture of (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-isobutyl)-succinyl-L-phenylalanine-N-methylamide (146 mg) and 10% Pd/C (50 mg) in 1:1 EtOH/THF (20 ml) was exposed to a hydrogen atmosphere for 3 hr. The catalyst was

removed by filtration (Celite filter aid) washing with additional ethanol, and the solvent was removed in vacuo, to leave the title compound (100 mg) as a white solid. FT-IR (KBr) 3321 br (NH), 1718-1697 br and 1646 (CO). NMR (200 MHz, DMSO-d_6) 0.79 (d, 6 H, J= 6.4), 1.10-1.50 (m, 3 H), 1.34 (s, 9 H), 2.46 (d, 3H, J= 4.8), 2.82 (m, 2 H), 3.94 (dd, 1 H, J= 8.8 and 6.2), 4.39 (m, 1 H), 6.52 (d, 1 H, J= 8.8), 7.20 (m, 5 H), 7.75 (m, 1 H), 8.22 (d, 1 H, J= 7.9), 12.60 (br s, 1 H) ppm.

EXAMPLE 2

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-25).

-Step (a): (3S-tert-Butoxycarbonylamino-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (300 mg), prepared as described in Example 1, was suspended in dry MeCN (30 ml) and treated under nitrogen with O-benzyl hydroxylamine hydrochloride (117 mg) and N-methylmorpholine (0.16 ml). After 10 min, TBTU (O-1H-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate; 258 mg) was added to the resulting clear solution, and the mixture let stir for 3 h. The solvent was removed in vacuo and the residue partitioned between dichloromethane and water. The organic phase was washed several times with water, dried and evaporated to leave a white solid, collected after trituration with diisopropyl ether, consisting of (4-benzyloxyamino-3S-tert-butoxycarbonylamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (320 mg).

-Step (b): The material from step (a) above (85 mg) was dissolved in DMF (5 ml) and treated under a hydrogen atmosphere for 30 min in the presence of 10% Pd/C (60 mg). The catalyst was removed by filtration (Celite filter aid), most of the solvent was removed in vacuo, and the residue was triturated with ethyl ether to obtain the title compound as a white powder (56 mg). FT-IR (KBr) 3314 (NHOH), 1686, 1662, and 1640 (CO) cm^{-1}. NMR (200 MHz, DMSO-d_6) 0.70 (two d, 6 H, J= 6.3), 0.84 (m, 1 H), 1.27 (s, 9 H), 1.18-1.48 (m, 2 H), 2.41 (d, 3 H), 2.60 (m, 1 H), 2.80 (m, 2 H), 3.79 (m, 1 H), 4.35 (m, 1 H), 6.50 (d, 1 H, J= 8.6), 7.06-7.21 (m, 5 H), 7.75 (m, 1 H), 7.98 (d, 1 H, J= 8.8), 8.80 (br s, 1 H), 10.70 (br s, 1 H) ppm. FAB-MS 465 $(MH)^+$, 365, 304, 179, 120 m/z.

EXAMPLE 3

(3S-Amino-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-1).

(3S-tert-Butoxycarbonylamino-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (20 mg), prepared as described in Example 1, was dissolved in 95% aqueous trifluoroacetic acid (2 ml), and the solution was let stand overnight at 0 °C. Toluene was added and evaporated in vacuo, repeating the process several times. The residue was triturated in ethyl ether to collect the title compound, trifluoroacetate salt, as a pale yellow powder. FT-IR (KBr) 3400-3300 br, 3294, 1745-1664 br cm^{-1}. NMR (400 MHz, DMSO-d_6) 0.77 (d, 6 H, J= 6.1), 1.25-1.45 (m, 3 H), 2.52 (d, 3 H, J= 4.6), 2.76 (m, 1 H), 2.84 (dd, 1 H, J= 13.9 and 8.8), 3.01 (dd, 1 H, J= 13.9 and 5.7), 3.73 (d, 1 H, J= 2.6), 4.36 (m, 1 H), 7.20 (m, 5 H), 7.99 (br s, 1 H), 8.64 (d, 1 H, J= 7.0) ppm.

EXAMPLE 4

(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-2).

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (30 mg), obtained as described in Example 2, was poured into 95% aqueous trifluoroacetic acid (3 ml) and stirred for 2 hr at 4 °C. After filtration (Celite filter aid) and washing with fresh TFA, the solution was evaporated in vacuo repeatedly with the aid of toluene to obtain the title product, trifluoroacetate salt, as a powder. FT-IR (KBr) 3292 (NHOH), 1722-1644 br (CO) cm^{-1}. NMR (200 MHz, DMSO-d_6) 0.69-0.73 (two d, 6 H, J= 6.4), 0.77-1.41 (m, 3 H), 2.47 (d, 3H, J= 4.6), 2.60 (m, 1 H), 2.95 (m, 2 H), 3.38 (m, 1 H), 4.34 (m, 1 H), 7.20 (m, 5 H), 7.60-8.00 (br s, NH_3^+), 7.95 (m, 1 H), 8.25 (d, 1 H, J= 7.5), 9.25 (br s, 1 H), 11.00 (br s, 1 H) ppm. FAB-MS 365 $(MH)^+$, 179, 120 m/z.

EXAMPLE 5

(4-Hydroxy-2R-isobutyl-3S-*p*-toluenesulfonylamino)succinyl-L-phenylalanine-N-methylamide (Compound I-43).

-Step (a): A solution of 4S-benzyloxycarbonyl-3R-isobutylazetidinone (400 mg), obtained as described in Example 1, step (a), in dichloromethane (10 ml) was treated with DMAP (4-dimethylaminopyridine; 25 mg) and *p*-toluenesulfonyl chloride (219 mg) at room temperature overnight under a nitrogen atmosphere.

After quenching with saturated aqueous $NaHCO_3$, the organic layer was collected, washed with aqueous 1M NH_4Cl , brine, and dried over Na_2SO_4 . Evaporation and fractionation by flash chromatography over silica (n-hexane / EtOAc) afforded a portion of unreacted starting material (50 mg) and then pure 4S-benzyloxycarbonyl-3R-isobutyl-1-(*p*-toluenesulfonyl)azetidinone (100 mg) as an oil. FT-IR ($CHCl_3$) 1802 (azetidinone CO), 1752 (ester CO) cm^{-1}. NMR (400 MHz, $CDCl_3$) 0.79 (d, 3H, J= 6.4), 0.88 (d, 3 H, J= 6.4), 1.54-1.72 (m, 3 H), 2.44 (s, 3 H), 3.20 (m, 1 H), 4.32 (d, 1 H, J= 3.2), 5.19 (s, 2 H), 7.31 (d, 2 H, J= 8.5), 7.33 (m, 5 H), 7.87 (d, 2 H, J= 8.5) ppm.

-Step (b): 4S-Benzyloxycarbonyl-3R-isobutyl-1-(*p*-toluenesulfonyl)-azetidinone from step (a) above (290 mg) was dissolved in dry DMF (15 ml). To this solution, L-phenylalanine-N-methylamide (p-toluenesulfonate salt; 486 mg), N-methylmorpholine (0.17 ml), and sodium azide (30 mg) were sequentially added. After overnight stirring at room temperature, the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with saturated aqueous $NaHSO_4$ and brine. Drying over Na_2SO_4 , evaporation, flash chromatography over silica, and trituration in ethyl ether afforded(4-benzyloxy-2R-isobutyl-3S-(*p*-toluenesulfonyl)amino)succinyl-L-phenylalanine -N-methylamide as a white powder (200 mg). FT-IR (KBr) 3330, 3255, 1750, 1721, 1650 cm^{-1}.

-Step (c): (4-Benzyloxy-2R-isobutyl-3S-(*p*-toluenesulfonyl)amino)succinyl-L-phenylalanine-N-methylamide (140 mg) from step (b) above was dissolved in a mixture of THF (20 ml) and DMF (2 ml). The resulting solution was treated with 10% Pd/C (100 mg) and exposed to a hydrogen atmosphere for 5 hr. The catalyst was removed by filtration (Celite filter aid) washing with additional THF, and the solvent was removed in vacuo to leave the title compound (110 mg) as a white solid. NMR (400 MHz, DMSO-d_6) 0.60 (d, 3 H, J= 6.8), 0.64 (d, 3 H, J= 6.8), 0.86 (m, 1 H), 1.07 (m, 1 H), 1.34 (m, 1 H), 2.28 (s, 3 H),

2.46 (d, 3 H, J= 4.7), 2.53 (m, 1 H), 2.70 (dd, 1 H, J= 13.7 and 8.1), 2.88 (dd, 1 H, J= 13.7 and 6.8), 3.71 (m, 1 H), 4.31 (m, 1 H), 7.18 (m, 5 H), 7.27 (d, 2 H, J= 8.1), 7.57 (d, 2 H, J= 8.1), 7.60 (br s, 1 H), 8.06 (d, 1 H, J= 8.1), 12.60 (br s, 1 H) ppm.

EXAMPLE 6

(4-Hydroxyamino-2R-isobutyl-3S-(*p*-toluenesulfonyl)amino)succinyl-L-phenylalanine-N-methylamide (Compound I-44).

-Step (a): (4-Hydroxy-2R-isobutyl-3S-(*p*-toluenesulfonyl)amino)succinyl-L-phenylalanine-N-methylamide (170 mg), prepared as described in Example 5, was suspended in dry MeCN (15 ml) and treated under nitrogen with O-benzyl hydroxylamine hydrochloride (64.7 mg) and N-methylmorpholine (0.1 ml). After 10 min, TBTU (O-1H-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate; 131 mg) was added to the resulting clear solution, and the mixture let stir for 5 h. The solvent was removed in vacuo and the residue partitioned between dichloromethane and water. The organic phase was sequentially washed with aqueous NH_4Cl, water and brine, dried, filtered and evaporated to leave crude (4-benzyloxyamino-2R-isobutyl-3S-(*p*-toluenesulfonyl)amino)-succinyl-L-phenylalanine-N-methylamide.

-Step (b): The material from step (a) above was dissolved in THF (15 ml) and treated under a hydrogen atmosphere for 5 hr in the presence of 10% Pd/C (100 mg). The catalyst was removed by filtration (Celite filter aid), the solvent was removed in vacuo, and the residue was triturated with a mixture of ethyl ether and dichlorometane to obtain the title compound as a white powder (50 mg). FT-IR (KBr) 3298 (NHOH), 1640 br (CO) cm^{-1}. NMR (400 MHz, DMSO-d_6) 0.64 (two d, 6 H, J= 6.4), 0.75 (m, 1 H), 1.12 (m, 1 H), 1.30 (m, 1 H), 2.27 (s, 3 H), 2.45 (s, 3 H), 2.65 (m, 1 H), 2.82 (m, 1 H), 3.62 (d, 1 H, J= 8.7), 4.25 (m, 1 H), 7.11-7.23 (m, 7 H), 7.55 (d, 2 H, J= 8.2) ppm.

EXAMPLE 7

(4-Hydroxy-2R-isobutyl-3S-(4-morpholinocarbonyl)amino)succinyl-L-phenylalanine-N-methylamide (Compound I-60).

-Step (a): A solution of 4S-benzyloxycarbonyl-3R-isobutylazetidinone (200 mg), obtained as described in Example 1, step (a), in dichloromethane (10 ml) was treated with triethylamine (0.44 ml), DMAP (4-dimethylaminopyridine; 10 mg) and 4-morpholinocarbonyl chloride (0.26 ml) at room temperature overnight under a nitrogen atmosphere.

After quenching with saturated aqueous $NaHCO_3$, the organic layer was collected, washed with aqueous 1M $KHSO_4$, brine, and dried over Na_2SO_4 . Evaporation and fractionation by flash chromatography over silica (n-hexane / EtOAc) afforded 4S-benzyloxycarbonyl-3R-isobutyl-1-(4-morpholinocarbonyl)azetidinone (170 mg) as a waxy solid. FT-IR ($CHCl_3$) 1787 (azetidinone CO), 1748 (ester CO), 1678 (urea CO) cm^{-1}. NMR (400 MHz, $CDCl_3$) 0.85 (d, 3H, J= 6.4), 0.93 (d, 3 H, J= 6.4), 1.60-1.83 (m, 3 H), 3.19 (m, 1 H), 3.53 (m, 2 H), 3.67 (m, 6 H), 4.36 (d, 1 H, J= 3.2), 5.16 (d, 1 H, J= 12.1), 5.28 (d, 1 H, J= 12.1), 7.35 (m, 5 H) ppm.

-*Step (b)*: 4S-Benzyloxycarbonyl-3R-isobutyl-1-(4-morpholinocarbonyl)azetidinone from step (a) above (170 mg) was dissolved in dry DMF (10 ml). To this solution, L-phenylalanine-N-methylamide (p-toluenesulfonate salt; 317 mg), N-methylmorpholine (0.11 ml), and sodium azide (20 mg) were sequentially added under a nitrogen atmosphere. After 6 hr at room temperature and overnight standing in the refrigerator, the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with water and brine. Drying over Na_2SO_4 and evaporation left crude (4-benzyloxy-2R-isobutyl-3S-(4-morpholinocarbonyl)amino)succinyl-L-phenyl-alanine-N-methylamide as a yellowish foam (207 mg). FT-IR (KBr) 3312 br, 1743, 1641 cm^{-1}.

-*Step (c)*: (4-Benzyloxy-2R-isobutyl-3S-(4-morpholinocarbonyl)amino)succinyl-L-phenylalanine-N-methylamide (200 mg) from step (b) above was dissolved in ethanol (10 ml). The resulting solution was treated with 10% Pd/C (100 mg) and exposed to a hydrogen atmosphere for 6 hr. The catalyst was removed by filtration (Celite filter aid) washing with additional EtOH and the solvent was removed in vacuo to leave the title compound (170 mg) as a white solid. NMR (200 MHz, DMSO-d_6) 0.72 (two d, 6 H, J= 6.2), 1.00-1.60 (m, 3 H), 2.44 (d, 3 H, J= 3.9), 2.60-2.95 (m, 3 H), 3.16 (m, 4 H), 3.48 (m, 4 H), 4.02 (dd, 1 H, J= 7.3 and 6.4), 4.33 (m, 1 H), 6.52 (d, 1 H, J= 7.9), 7.20 (m, 5 H), 7.87 (br s, 1 H), 8.38 (br s, 1 H) ppm.

EXAMPLE 8

(4-Hydr xyamino-2R-isobutyl-3S-(4-morpholin carbonyl)amino)succinyl-L-phenylalanine-N-methylamide (Compound I-61).

-Step (a): (4-Hydroxy-2R-isobutyl-3S-(4-morpholinocarbonyl)amino)succinyl-L-phenylalanine-N-methylamide (120 mg), prepared as described in Example 7, was suspended in dry MeCN (20 ml) and treated under nitrogen with O-benzyl hydroxylamine hydrochloride (41 mg) and N-methylmorpholine (0.06 ml). After 10 min. TBTU (O-1H-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate; 100 mg) was added to the resulting clear solution, and the mixture let stir for 5 h. The solvent was removed in vacuo and the residue partitioned between dichloromethane and water. The organic phase was sequentially washed with aqueous NH_4Cl, water and brine, dried, filtered and evaporated to leave crude (4-benzyloxyamino-2R-isobutyl-3S-(4-morpholinocarbonyl)amino)-succinyl-L-phenylalanine-N-methylamide (130 mg) as a white solid.

-Step (b): The material from step (a) above was dissolved in ethanol (15 ml) and THF (5 ml) and treated under a hydrogen atmosphere for 3 hr in the presence of 10% Pd/C (100 mg). The catalyst was removed by filtration (Celite filter aid), the solvent was removed in vacuo, and the residue was triturated with ethyl ether to obtain the crude title compound as a pink solid (92 mg), which was further purified by silica gel chromatography (9:1 dichlorometane-methanol). FT-IR (KBr) 3313 (NHOH), 1694 and 1628 br (CO) cm^{-1}. NMR (400 MHz, DMSO-d_6) 0.72 (d, 3 H, J= 6.4), 0.73 (d, 3 H, J= 6.4), 0.87 (m, 1 H), 1.28 (m, 1 H), 1.45 (m, 1 H), 2.41 (d, 3 H, J= 4.7), 2.69 (m, 1 H), 2.73 (dd, 1 H, J= 13.6 and 6.5), 2.83 (dd, 1 H, J= 13.6 and 7.8), 3.08-3.24 (m, 4 H), 3.42-3.51 (m, 4H), 3.98 (dd, 1 H, J= 8.7 and 8.7), 4.36 (m, 1 H), 6.40 (d, 1 H), 7.05-7.22 (m, 5 H), 7.64 (q, 1 H, J= 4.7), 7.92 (d, 1 H, J= 8.1), 8.78 (br s, 1 H), 10.60 (br s, 1 H) ppm.

EXAMPLE 9

(3S-Benzamido-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-71).

-Step (a): A solution of 4S-benzyloxycarbonyl-3R-isobutylazetidinone (300 mg), obtained as described in Example 1, step (a), in dichloromethane (10 ml) was treated with triethylamine (0.5 ml) and benzoyl chloride (0.4 ml) at 0 °C and the at room temperature

overnight under a nitrogen atmosphere.

The reaction mixture was diluted with dichloromethane, washed several times with aqueous $NaHCO_3$, and then with 1M $KHSO_4$ and brine. After drying over Na_2SO_4 , evaporation and fractionation by flash chromatography over silica (n-hexane / EtOAc), 1-benzoyl-4S-benzyloxycarbonyl-3R-isobutylazetidinone (235 mg) was obtained as a powder. FT-IR (KBr) 1801, 1749, 1678 cm^{-1}. NMR (200 MHz, $CDCl_3$) 0.86 (d, 3 H, J= 6.0), 0.94 (d, 3 H, J= 6.0), 1.60-1.90 (m, 3 H), 3.30 (m, 1 H), 4.37 (d, 1 H), 5.22-5.31 (Abq, 2 H, J= 12.0), 7.35-7.64 (m, 8 H), 8.05 (m, 2 H) ppm.

-Step (b): 1-Benzoyl-4S-benzyloxycarbonyl-3R-isobutylazetidinone from step (a) above (235 mg) was dissolved in dry DMF (10 ml). To this solution, L-phenylalanine-N-methylamide (p-toluenesulfonate salt; 450 mg), N-methylmorpholine (0.16 ml), and sodium azide (20 mg) were sequentially added under a nitrogen atmosphere. After 6 hr at room temperature the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with 1 N aqueous NH_4Cl and brine. After drying over Na_2SO_4 and evaporation of the solvent, the residue was purified by flash chromatography over silica (n-hexane / EtOAc) to afford (3S-benzamido-4-benzyloxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide as a white powder (330 mg). FT-IR (KBr) 3299, 1734, 1655-1639 br cm^{-1}.

-Step (c): (3S-Benzamido-4-benzyloxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (330 mg) from step (b) above was dissolved in 1:1 ethanol-THF (10 ml). The resulting solution was treated with 10% Pd/C (150 mg) and exposed to a hydrogen atmosphere for 4 hr. The catalyst was removed by filtration (Celite filter aid) washing with additional EtOH and the solvent was removed in vacuo to leave the title compound (250 mg) as a white solid. FT-IR (KBr) 3297, 1719, 1635 br cm^{-1}. NMR (200 MHz, DMSO-d_6) 0.63 (d, 3 H, J= 6.3), 0.72 (d, 3 H, J= 6.3), 1.20 (m, 2 H), 1.41 (m, 1 H), 2.51 (d, 3 H, J= 4.7), 2.80 (m, 2 H), 2.99 (m, 1 H), 4.30 (m, 2 H), 7.20 (m, 4 H), 7.50 (m, 4 H), 7.72 (m, 2 H), 8.10 (d, 1 H, J= 5.9), 8.27 (m, 1 H), 8.76 (d, 1 H, J= 8.3) ppm.

EXAMPLE 10

(3S-Benzamido-4-hydr xyamino-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (Compound I-72).

By the same procedure described in Example 2, steps (a) and (b), starting from (3S-benzamido-4-hydroxy-2R-isobutyl)succinyl-L-phenylalanine-N-methylamide (prepared as described in Example 9), the title compound was obtained. FAB-MS 469 (27, $(MH)^+$), 436 (20, $(MH - NH_2OH)^+$. 179 (45, $(PheNHMe + H)^+$), 105 (100. $(PhCO)^+$) m/z.

EXAMPLE 11

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-phenylpropyl)succinyl-L-phenylalanine-N-2-(4-morpholino)ethyl amide (Compound III-86).

-Step (a): A solution of 1-tert-butyldimethylsilyl-4S-carboxyazetidinone (0.7 g) in dry THF (20 ml) was treated dropwise at 0-5 °C with a 2M solution of LDA (3.2 ml) in the same solvent, to obtain an orange solution of the di-anion. After 10 min, a solution of cinnamyl bromide (1.4 g) in THF (2 ml) was added at 0 °C under stirring, and the resulting solution was left at the same temperature overnight. Quenching with 1M aqueous $KHSO_4$ (300 ml), followed by extraction with EtOAc, afforded crude 1-tert-butyldimethylsilyl-4S-carboxy-3R-cinnamylazetidinone as a syrup.

The above material was dissolved in dry DMF (5 ml) and treated dropwise, in this order, with triethylamine (0.5 ml) and benzyl bromide (0.46 ml). After 4 hr at room temperature, the mixture was partitioned between water and EtOAc. The organic phase, after washing with saturated aqueous NaCl, was dried and evaporated to obtain crude 4S-benzyloxycarbonyl-1-tert-butyldimethylsilyl-3R-cinnamylazetidinone, which was dissolved in THF (5 ml) and left 3 h in the presence of tetrabutylammonium fluoride trihydrate (1.1.6 g) and acetic acid (0.84 ml). The mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, the organic phase was collected, washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography over silica gel (n-hexane/EtOAc) afforded 4S-benzyloxycarbonyl-3R-cinnamylazetidinone (0.45 g) as a white powder. NMR (200 MHz, $CDCl_3$) 1.45 (s, 9 H), 2.70 (m, 2 H), 3.30 (m, 1 H), 4.22 (d, 1 H, J= 3.1), 5.15 and 5.25 (two d, 2 H, J= 12.1), 6.20 (m, 1 H), 6.60 (m, 1 H), 7.2-7.3 (m, 10 H) ppm.

-Step (b): A solution of 4S-benzyloxycarbonyl-3R-cinnamylazetidinone (0.44 g) from step (a) above in MeCN (10 ml) was treated with DMAP (0.2 g) and BOC_2O (0.75 g) at 40 °C for 1 h. A second portion of BOC_2O (0.35 g) was added, and after additional 10 min at 40 °C the mixture was diluted with ethyl acetate, and sequentially washed with aqueous 1M $KHSO_4$, saturated $NaHCO_3$, and brine. Drying over Na_2SO_4 and evaporation left crude 4S-benzyloxycarbonyl-1-tert-butoxycarbonyl-3R-cinnamylazetidinone (0.7 g) as a syrup.

-Step (c): Crude 4S-benzyloxycarbonyl-1-tert-butoxycarbonyl-3R-cinnamyl-azetidinone from step (b) above (0.28 g) was dissolved in dry DMF (3 ml). To this solution, L-phenylalanine-N-2-(4-morpholino)ethylamide (425 mg), N-methyl-morpholine (0.19 ml), and sodium azide (35 mg) were sequentially added. After overnight stirring at room temperature, the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with water and brine. Drying over Na_2SO_4 , evaporation and flash chromatography over silica afforded (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-cinnamyl)succinyl-L-phenylalanine-N-2-(4-morpholino)ethylamide (300 mg). NMR (400 MHz, DMSO-d_6) 1.36 (s, 9 H), 2.15 (m, 2 H), 2.25 (m, 4 H), 2.30 (m, 2 H), 2.75 and 2.90 (two m, 2 H), 2.90-3.1 (m, 3 H), 3.50 (m, 4 H), 4.20 (m, 1 H), 4.45 (m, 1 H), 4.95 (m, 2 H), 6.10 (m, 1 H), 6.30 (m, 1 H), 6.70 (d, 1 H, J= 7.5), 7.0-7.4 (m, 15 H), 7.76 (broad s, 1 H), 8.40 (broad s, 1 H) ppm.

-Step (d): A mixture of (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-cinnamyl)-succinyl-L-phenylalanine-N-2-(4-morpholino)ethylamide (300 mg) and 10% Pd/C (100 mg) in 1:1 EtOH/THF (40 ml) was exposed to a hydrogen atmosphere for 3 hr. The catalyst was removed by filtration (Celite filter aid) washing with additional ethanol, and the solvent was removed in vacuo, to leave crude (3S-tert-butoxycarbonylamino-4-hydroxy-2R-phenylpropyl)succinyl-L-phenylalanine-N-2-(4-morpholino)ethylamide as a white solid.

-Step (e): The crude material from step (d) above was treated O-benzyl hydroxylamine hydrochloride, N-methylmorpholine and TBTU in the same manner as described in Example 2, step (a). Workup and chromatography afforded (4-benzyloxyamino-3S-tert-butoxycarbonylamino-2R-phenylpropyl)succinyl-L-phenylalanine-N-2-(4-morpholino)ethylamide (220 mg).

-Step (f): The material from step (e) above (145 mg) was dissolved in DMF (5 ml) and treated under a hydrogen atmosphere for 30 min in the presence of 10% Pd/C (60 mg). The catalyst was removed by filtration (Celite filter aid), most of the solvent was removed in vacuo, and the residue was triturated with ethyl ether to obtain the title compound as a white powder (90 mg). FT-IR (KBr) 3315 (NHOH), 1685, 1660, and 1640 (CO) cm^{-1}

EXAMPLE 12

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-isobutyl)succinyl-(S)-tert-butylglycine methyl ester (Compound IV-64).

-Step (a): 4S-Benzyloxycarbonyl-1-tert-butoxycarbonyl-3R-isobutylazetidinone (200 mg), obtained as described in Example 1, step (b), was dissolved in dry DMF (4 ml). To this solution, (S)-tert-butylglycine methyl ester (160 mg), N-methylmorpholine (0.05 ml), and sodium azide (25 mg) were sequentially added. After overnight stirring at room temperature, the solvent was partially removed in vacuo and the residue, taken up in EtOAc, was sequentially washed with water and brine. Drying over Na_2SO_4, evaporation and flash chromatography over silica afforded (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-isobutyl)succinyl-(S)-tert-butylglycine methyl ester as a white powder (260 mg). FT-IR (KBr) 3375 br (NH), 1737, 1718, and 1664 (CO) cm^{-1}.

-Step (b): A mixture of (4-benzyloxy-3S-tert-butoxycarbonylamino-2R-isobutyl)-succinyl-(S)-tert-butylglycine methyl ester (260 mg) and 10% Pd/C (100 mg) in 1:2 EtOH/THF (10 ml) was exposed to a hydrogen atmosphere for 5 h. The catalyst was removed by filtration (Celite filter aid) washing with additional ethanol, and the solvent was removed in vacuo, to afford (3S-tert-butoxycarbonylamino-4-hydroxy-2R-isobutyl)succinyl-(S)-tert-butylglycine methyl ester (210 mg) as a yellowish waxy solid. FT-IR (KBr) 3372 (OH), 1720, 1686, and 1655 (CO) cm^{-1}. NMR (200 MHz, DMSO-d_6) 0.81 (d, 3 H, J= 6.4), 0.83 (d, 3 H, J= 6.4), 0.91 (s, 9 H), 1.00-1.60 (m, 3 H), 1.33 (s, 9 H), 2.96 (m, 1 H), 3.59 (s, 3 H), 3.89 (dd, 1 H, J= 8.8 and 6.9), 4.12 (d, 1 H, J= 8.3), 6.46 (d, 1 H, J= 8.8), 8.13 (broad s, 1 H), 12.67 (broad s, 1 H) ppm.

-Step (c): The material from step (b) above (195 mg) was dissolved in dry MeCN (5 ml) and treated under nitrogen with O-benzyl hydroxylamine hydrochloride (90 mg) and N-methylmorpholine (0.13 ml). After 10 min, TBTU (180 mg) was added, and the mixture let stir for 6 h. The solvent was removed in vacuo and the residue partitioned between dichloromethane and aqueous 0.2 N HCl. The organic phase was washed with brine, dried

and evaporated to leave a residue, which was purified by silica gel chromatography, thereby obtaining (4-benzyloxyamino-3S-tert-butoxycarbonylamino-2R-isobutyl) succinyl -(S)-tert-butylglycine methyl ester (170 mg) as a white solid.

-Step (d): The material from step (c) above (170 mg) was dissolved in ethanol (5 ml) and treated under a hydrogen atmosphere for 2 h in the presence of 10% Pd/C (100 mg). The catalyst was removed by filtration (Celite filter aid), washing with additional ethanol, and the combined solution was evaporated to dryness, thereby obtaining the title product as a white powder (90 mg). NMR (200 MHz, DMSO-d_6) 0.76 (d, 6 H, J= 6.4), 0.92 (s, 9 H), 1.29 (s, 9 H), 1.20-1.60 (m, 3 H), 2.80 (m, 1 H), 3.58 (s, 3 H), 3.72 (dd, 1 H, J= 8.8 and 8.8), 4.14 (d, 1 H, J= 8.6), 6.47 (d, 1 H, J= 8.8), 7.73 (d, 1 H, J= 8.6), 8.89 (broad s, 1 H), 10.70 (broad s, 1 H) ppm.

EXAMPLE 13

(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl-(S)-tert-butylglycine methyl ester (Compound IV-65).

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-isobutyl)succinyl-(S)-glycine methyl ester (40 mg), prepared as described in Example 12, was dissolved in 95% aqueous trifluoroacetic acid (3 ml). After 20 min, the mixture was evaporated. Toluene was added and evaporated two times. The residue was triturated in ethyl ether to collect the title compound, trifluoroacetate salt, as a pale pink powder (40 mg). FT-IR (KBr) 3363 (NHOH), 1717, 1685 br (CO) cm^{-1}.). NMR (400 MHz, DMSO-d_6) 0.78 and 0.82 (each d, 6 H, J= 6.4), 0.91 (s, 9 H), 1.10-1.5 (m, 3 H), 2.95 (m, 1 H), 3.45 (m, 1 H), 3.54 (s, 3 H), 3.99 (d, 1 H, J= 7.0), 8.08 (d, 1 H, J= 7.0), 8.10 (broad s, 1 H), 9.30 and 9.50 (respectively, broad s, major, and s, minor; 1 H), 10.70 and 11.03 (respectively, minor and major; each s, 1 H) ppm. Note: the compound exists in DMSO solution as a mixture of two rotamers; minor and major signals indicated.

In the following Examples, other compounds were analogously prepared:

EXAMPLE 14

(3S-tert-Butoxycarbonylamino-4-hydroxy-2R-phenylpropyl)succinyl-L-phenyl-alanine-N-methyl amide.

White powder. NMR (200 MHz, DMSO-d_6) 1.46 (s, 9 H), 1.60 (m, 4 H), 2.58 (t, 2H, J= 6.7), 2.64 (d, 3 H, J= 4.8), 2.93 (m, 2H), 3.14 (dd, 1 H, J= 13.4 and 5.4), 4.34 (dd, 1 H, J= 2.5 and 6.1), 4.44 (m, 1 H), 5.30 (m, 1 H), 5.98 (d, 1 H, J= 6.1), 7.1-7.3 (m, 10 H) ppm.

EXAMPLE 15

(3S-Amino-4-hydr xy-2R-phenylpropyl)succinyl-L-phenylalanine-N-methyl amide.

Obtained as the trifluoroacetate salt: white powder. NMR (200 MHz, DMSO-d_6) 1.2-1.5 (m, 4 H), 2.39 (t, 2H, J= 7.9), 2.50 (d, 3 H, J= 4.4), 2.52 (m, 1 H), 2.79 (dd, 1 H, J= 13.4 and 10.8), 3.09 (dd, 1 H, J= 3.5 and 13.4), 3.46 (d, 1 H, J= 2.6), 4.26 (m, 1 H), 7.1-7.3 (m, 10 H), 8.46 (broad s, 1 H), 9.00 (d, 1 H, J= 8.4) ppm.

EXAMPLE 16

(3S-tert-Butoxycarbonylamino-4-hydroxyamino-2R-phenylpropyl)succinyl-L-phenylalanine-N-methyl amide (Compound III-87).

White powder. NMR (400 MHz, DMSO-d_6) 1.28 (s, 9 H), 1.1-1.5 (m, 4 H), 2.35 (m, 2H), 2.38 (d, 3 H, J= 4.3), 2.57 (m, 1 H), 2.82 (m, 2 H), 3.83 (dd, 1 H, J= 8.7 and 8.7), 4.34 (m, 1 H), 6.52 (d, 1 H, J= 8.7), 7.1-7.2 (m, 10 H), 7.72 (q, 1 H, J= 4.3), 8.01 (d, 1 H, J= 8.1), 8.85 (s, 1 H), 10.71 (s, 1 H) ppm.

EXAMPLE 17

(3S-Amino-4-hydroxyamino-2R-phenylpropyl)succinyl-L-phenylalanine-N-methyl amide (Compound III-88).

Obtained as the trifluoroacetate salt: white powder. NMR (400 MHz, DMSO-d_6) 1.40 (m, 4 H), 2.4-2.5 (m, 3H), 2.44 (s, 3 H), 4.34 (m, 1 H), 7.20 (m, 10 H), 7.9-8.4 (3 broad s, 5H: CONH, CONHMe and NH_3^+), 9.2 (broad s, 1 H), 10.9 (broad s, 1 H) ppm.

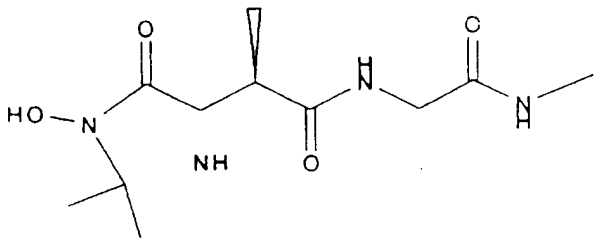
EXAMPLE 18

(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl-L-phenylalanine-N-tert-butyl amide (Compound I-21).

Obtained as the trifluoroacetate salt; white powder. NMR (400 MHz, DMSO-d_6) 0.78 and 0.80 (each d, 6 H, J= 6.8), 1.10 and 1.5 (each m, 2 H), 1.11 (s, 9 H), 1.40 (m, 1 H), 2.70 (m, 1 H), 2.89 (d, 2 H, J= 7.3), 3.50 (m, 1 H), 4.47 (dt, 1 H, J= 7.3, 7.3 and 8.6), 7.20 (m, 5 H), 7.40 (s, 1 H), 8.20 (broad s, 1 H), 8.23 (d, 1 H, J= 8.6), 9.37 and 9.53 (respectively, broad s, major, and s, minor; 1 H), 10.76 and 11.09 (respectively, minor and major; each s, 1 H) ppm. Note: the compound exists in DMSO solution as a mixture (ca 5:1) of two rotamers; minor and major signals indicated.

EXAMPLE 19

(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl-L-phenylalanine-N-methyl amide, cyclic acetone diaminal.



Obtained (trifluoroacetate salt) from the compound of Example 18 by stirring with neat acetone, and evaporation to dryness in vacuo. White powder. NMR (400 MHz, DMSO-d_6) 0.75 and 0.80 (each d, 6 H, J= 6.8), 1.13 and 1.19 (each s, 6 H), 1.14 (s, 9 H), 1.2-1.6 (m, 3 H), 2.55 (m, 1 H), 2.78 (dd, 1 H, J= 8.1 and 13.7), 2.88 (dd, 1 H, J= 6.0 and 13.7), 2.99 (d, J= 8.5), 3.30 (m, 1 H, overlapped by water), 4.40 (ddd, 1 H, J= 6.0, 8.1 and 8.1), 7.21 (m, 6 H), 8.13 (d, 1 H, J= 8.1), 9.53 (s, 1 H) ppm.

EXAMPLE 20

(3S-Dimethylamino-4-hydroxyamino-2R-isobutyl)succinyl-(S)-tert-butylglycine-N-methyl amide (Compound II-122).

Obtained as the free base; white powder. NMR (400 MHz, DMSO-d_6) 0.73 and 0.81 (each d, 6 H, J= 6.5), 0.88 (s, 9 H), 0.9-1.4 (m, 3 H), 2.18 (s, 6 H), 2.53 (d, 3 H, J= 4.4), 2.80 (m, 2 H), 4.22 (d, 1 H, J= 9.4), 7.26 (d, 1 H, J= 9.4), 7.79 (q, 1 H, J= 4.4), 8.78 (s, 1 H), 10.41 (s, 1 H) ppm.

EXAMPLE 21

(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl-(S)-tert-butylglycine-N-(4-pyridyl) amide (Compound IV-2).

Obtained as the double trifluoroacetate salt; white powder. NMR (400 MHz, DMSO-d_6) 0.76 and 0.83 (each d, 6 H, J= 6.5), 0.96 and 0.99 (respectively, minor and major; each s, 9 H), 1.1-1.5 (m, 3 H), 3.03 and 3.30 (respectively, major and minor; each m, 1 H), 3.58 and 4.20 (respectively, major, d, J= 6.4, and minor, broad s; 1H), 4.27 and 4.30 (respectively, major and minor; each d, J= 7.3), 7.88 (d, 2 H, J= 6.8), 8.15 (broad s, 3 H), 8.60 (d, 2 H, J= 6.8), 9.32 and 9.55 (respectively, major, broad s, and minor, s; 1 H), 10.77 and 11.03

(respectively, major and minor: each s, 1 H), 11.12 (s, 1 H) ppm. Note: the compound exists in DMSO solution as a mixture (ca 4:1) of two rotamers; minor and major signals indicated.

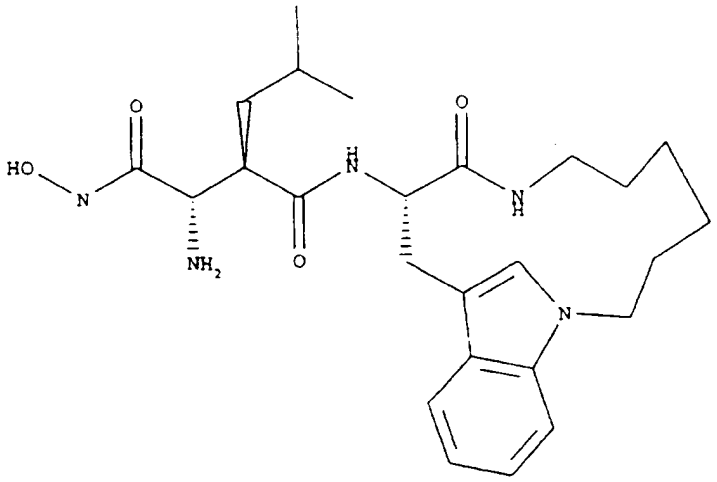
EXAMPLE 22

(3S-Amino-2R-cyclopentylmethyl-4-hydroxyamino)succinyl-(S)-tert-butylglycine-N-(3,4-methylenedioxyphenyl) amide (Compound IV-41).

Obtained as the trifluoroacetate salt; white powder. NMR (400 MHz, DMSO-d_6) 0.89 and 0.92 (respectively, minor and major; each s, 9 H), 1.2-1.8 (m, 11 H), 2.93 (m, 1 H), 3.58 (m, 1 H), 4.28 (d, J= 9.4), 5.92 (m, 2 H), 6.80 (d, 1 H, J= 8.2), 6.88 (dd, 1 H, J= 2.0 and 8.2), 7.20 (d, 1 H, J= 2.0), 7.85 and 8.10 (respectively, minor and major; each broad s, 3 H of NH_3^+), 7.90 and 7.97 (respectively, minor, d, J= 9.0, and major, d, J= 9.4; 1 H of CONHCH), 9.26 and 9.35 (respectively, major and minor: each s, 1 H of CONHOH), 9.93 and 10.01 (respectively, major and minor, each s, 1 H of CONHAr), 10.72 and 10.96 (respectively, minor and major; each s, 1 H of CONHOH) ppm. Note: the compound exists in DMSO solution as a mixture (ca 4:1) of two rotamers; minor and major signals indicated.

EXAMPLE 23

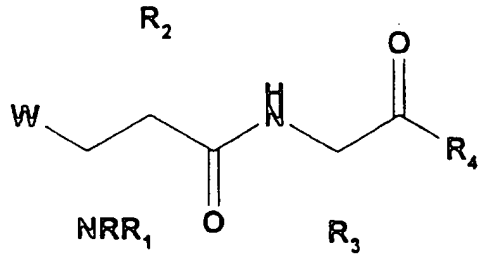
10(S)-[(3S-Amino-4-hydroxyamino-2R-isobutyl)succinyl]amino-1.8-diazatricyclo-[10,6,1,$0^{13,18}$]-nonadeca-12(19),13(18),14,16-tetraen-9-one (Compound II-102).



Obtained as the trifluoroacetate salt; white powder. NMR (400 MHz, DMSO-d_6) -0.03 and 0.49 (each m, 2H of N-$(CH_2)_3$-CH_2-$(CH_2)_2$-NHCO), 0.81 and 0.83 (each d, J= 6.8, 6 H), 1.0-1.4 (m, 4 H of N-$(CH_2)_2$-CH_2-CH_2-CH_2-CH_2-NHCO), 1.10 and 1.50 (each m, 2 H), 1.40 (m, 1 H), 1.60 and 1.80 (each m, 2 H of N-CH_2-CH_2-$(CH_2)_4$-NHCO), 2.30 and 3.30 (each m, 2 H of N-$(CH_2)_5$-CH_2-NHCO), 2.85 (m, 2 H of CH-iBu and CHH-indanyl), 3.08 (dd, J= 3.8 and 13.7, 1 H of CHH-indanyl), 3.60 (m, 1 H of $CHNH_3^+$), 4.00 and 4.28 (each m, 2 H of N-CH_2-$(CH_2)_5$-NHCO), 4.50 (m, 1 H), 7.02 and 7.11 (each m, 2H of 6- and 7-indanyl), 7.07 (s, 1 H of 2-indanyl), 7.37 (m, 1 H of N-$(CH_2)_6$-NHCO), 7.41 (m, 1 H of 8-indanyl), 7.61 (m, 1 H of 5-indanyl), 8.00 and 8.20 (respectively, minor and major; each broad s, 3 H of NH_3^+), 8.37 (d, J= 8.1), 9.37 and 9.50 (respectively, major and minor; each s, 1 H of CONHOH), 10.84 and 11.09 (respectively, minor and major, each s, 1 H of CONHOH) ppm. Note: the compound exists in DMSO solution as a mixture (ca 84:16) of two rotamers; minor and major signals indicated.

CLAIMS

1. A compound which is a succinic amide derivative of formula (I)



(I)

wherein

W is a -COOH or -CONHOH group;

R is either hydrogen, C_1 - C_6 alkyl, phenyl, or benzyl;

R_1 is either hydrogen or:

- lower alkyl, especially methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl; aryl, especially phenyl and naphthyl; and aryl-(lower alkyl), especially benzyl; these groups being either unsubstituted or substituted by one or more substituents, equal or different, selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group $-(CH_2)_m$-heterocyclyl or $-(CH_2)_m$-cyclopropyl, wherein m is either zero, or an integer from one to three, and heterocyclyl represents a 3 to 6 membered heterocyclyl ring, simple or condensed with a benzene or naphthalene ring, containing at least one nitrogen atom; still preferably succinimido, phthalimido, saccharin, hydantoin, indolyl, oxyindolyl, 2-oxo-isoindolinyl, imidazolyl, pyridyl, morpholino, pyrrolidino, 2-oxopyrrolidino, piperazino; and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-(CH_2)_nCOOH$ or a group $-(CH_2)_mCOOR^1$, wherein n may be 1, 2 or 3, m may be 0, 1, 2 or 3, and R^1 is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, phenyl, benzyl, allyl, styryl, 1-naphthyl, 2-naphthyl, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo,

nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group selected from $-(CH_2)_mSO_2R^I$, $-(CH_2)_mSO_2NH_2$, $-(CH_2)_mSO_2N(Me)_2$, $-(CH_2)_mSO_2NHR^I$, wherein m, R^I and possible substituents of such R^I group are as defined above, or a group $-(CH_2)_mSO_2$-(4-morpholino), $-(CH_2)_mSO_2$-(1-piperazino), $-(CH_2)_mSO_2$-(4-methyl-1-piperazino); or

- a group $-(CH_2)_nSO_3H$, wherein n is as defined above;

- acyl, especially acetyl, or benzoyl, or phenacetyl, either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}-C(O)R^{III}$, wherein $-R^{II}-$ is selected from a chemical bond, $-CH_2-$, $-CH_2(CH_2)_mCH_2-$ wherein m is as defined above, $-CH=CH-$, $-CH_2CH=CH-$, phenylene (i.e., $-C_6H_4-$), $-CH_2CH=CH-C_6H_4-$, $-CH_2CH_2CH=CH-$, $-CH_2-CC-$, $-CH_2CH_2-CC-$, $-CH_2CH_2CH=CH-C_6H_4-$, $-CH_2-CC-C_6H_4-$, $-CH_2CH_2-CC-C_6H_4-$, and R^{III} is selected from methyl, ethyl, phenyl, hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, and morpholino; or

- a group -C(O)-heterocyclyl, wherein heterocyclyl is as defined above, and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}$-heterocyclyl or $-C(O)-R^{II}$-aryl, wherein R^{II}, heterocyclyl, aryl and possible substituents of such heterocyclyl or aryl are as described above; or

R and R_1, taken together with the nitrogen atom to which they are attached, represent morpholino, pyrrolidino, piperazino, N-methylpiperazino, succinimido, or phthalimido;

R_2 is C_3 -C_{15} linear or branched alkyl, either unsubstituted or substituted by a C_3 -C_7 cycloalkyl group; or

R_2 is C_3 -C_{15} linear or branched alkyl, either unsubstituted or substituted by a C_3 -C_7 cycloalkyl group; or

R_2 is a group $-R^{II}-H$, wherein R^{II} is as defined above, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, C_3 -C_4 linear or branched alkyl, fluoro, chloro, C_1-C_4 alkoxy, nitro, amino, dimethylamino, carboxy, carboxymethyl; or

R_2 is a group $-R^{II}-X-R^{IV}$, wherein R^{II} is as defined above. R^{IV} is C_1 -C_6 alkyl, C_3-C_7 cicloalkyl, C_2 -C_6 alkenyl, phenyl, phenyl (C_1 -C_6)alkyl, or phenyl (C_2 -C_6)alkenyl, either unsubstituted or substituted by a group selected from F, Cl, Br, C_1 -C_4 alkyl, C_1 -C_4 alkoxy, and X is either a direct bond, or an oxygen atom, a sulfur atom, or a sulfinyl -S(O)-, sulfonyl $-S(O)_2$ or carbamoyl group -CONH- or -NHCO-;

R_3 is the characterizing group of a natural or non-natural alpha-amino acid in which any functional group, if present, may be protected;

R_4 is either O-alkyl, wherein alkyl is a C_1 -C_4 straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 -C_4 straight or branched alkyl, chloro and methoxy; or

R_4 is $-NH_2$, -NH(C_1 -C_6 alkyl), -NH-aryl, -NH-heterocyclyl; or

R_4 is -NH(C_1 -C_6 alkyl) substituted by phenyl or heterocyclyl; or

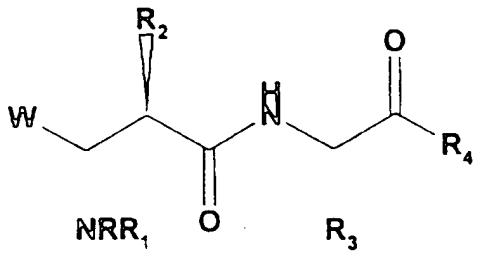
R_4 is -NH(C_2 -C_6 alkyl) substituted by a group selected from $-CONH_2$, $-NHCONH_2$, $-SO_2NH_2$, $-NHSO_2NH_2$, or derivatives thereof wherein the terminal nitrogen atom is substituted by one or two methyl groups, or derivatives thereof wherein the terminal nitrogen atom is part of a morpholino, pyrrolidino, piperazino, or N-methylpiperazino ring; or

R_4 is -NH(C_2 -C_6 alkyl) substituted by amino, protected amino, mono (C_1-C_6) alkylamino, di (C_1 -C_6) alkylamino, guanidino, morpholino, piperazino or N-methylpiperazino; or

R_3 and R_4 taken together are a group of the formula $-(CH_2)_m$-NH-, where m is from 5 to 12, optionally interrupted by a $-NR_5$ - group, wherein R_5 is selected from hydrogen, C_1 -C_6 alkyl, C_1 -C_6 alkoxycarbonyl, aryl, aryl (C_1 -C_6)alkyl, or aryl (C_1 -C_6) alkoxycarbonyl, or interrupted by a group $-C_6H_4$-O-, or interrupted by an indole ring linked through its C-3 and nitrogen atoms;

and wherein the alkyl, alkenyl, phenyl, cycloalkyl, heterocyclyl and characterizing groups in any of the above definitions of R_1, R_2, R_3, R_4, and A can be either unsubstituted or substituted by one or more substituents; and the salts, prodrugs, solvates and hydrates thereof, with the proviso that, when $-NRR_1$ is $-NH_2$, protected amino or acylamino, R_3 is tert-butyl and R_4 is either amino or alkylamino, then R_2 is different from isobutyl.

2. A compound as claimed in claim 1 having the formula (I'):



(I')

wherein:

W is a -COOH or -CONHOH group;

R is either hydrogen, methyl, ethyl, or benzyl;

R_1 is either hydrogen or:

- lower alkyl, especially methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl; aryl, especially phenyl and naphthyl; and aryl-(lower alkyl), especially benzyl; these groups being either unsubstituted or substituted by one or more substituents, equal or different, selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group $-(CH_2)_m$-heterocyclyl or $-(CH_2)_m$-cyclopropyl, wherein m is either zero, or an integer from one to three, and heterocyclyl represents a 3 to 6 membered heterocyclyl ring, simple or condensed with a benzene or naphthalene ring, containing at least one nitrogen atom; still preferably succinimido, phthalimido, saccharin, hydantoin, indolyl, oxyindolyl, 2-oxo-isoindolinyl, imidazolyl, pyridyl, morpholino, pyrrolidino, 2-oxopyrrolidino, piperazino; and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-(CH_2)_nCOOH$ or a group $-(CH_2)_mCOOR^1$, wherein n may be 1, 2 or 3, m may be 0, 1, 2 or 3, and R^1 is methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, phenyl, benzyl, allyl, styryl, 1-naphthyl, 2-naphthyl, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, isopropyl, tert-butyl, fluoro, chloro, bromo, nitro, amino, dimethylamino, hydroxy, methoxy, ethoxy, acetyl, acetamido, carboxy, carboxymethyl; or

- a group selected from $-(CH_2)_mSO_2R^I$, $-(CH_2)_mSO_2NH_2$, $-(CH_2)_mSO_2N(Me)_2$, $-(CH_2)_mSO_2NHR^I$, wherein m, R^I and possible substituents of such R^I group are as defined above, or a group $-(CH_2)_mSO_2$-(4-morpholino), $-(CH_2)_mSO_2$-(1-piperazino), $-(CH_2)_mSO_2$-(4-methyl-1-piperazino); or

- a group $-(CH_2)_nSO_3H$, wherein n is as defined above;

- acyl, especially acetyl, or benzoyl, or phenacetyl, either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}-C(O)R^{III}$, wherein $-R^{II}-$ is selected from a chemical bond, $-CH_2-$, $-CH_2(CH_2)_mCH_2-$ wherein m is as defined above, -CH=CH-, $-CH_2CH=CH-$, phenylene (i.e., $-C_6H_4-$), $-CH_2CH=CH-C_6H_4-$, $-CH_2CH_2CH=CH-$, $-CH_2-CC-$, $-CH_2CH_2-CC-$, $-CH_2CH_2CH=CH-C_6H_4-$, $-CH_2-CC-C_6H_4-$, $-CH_2CH_2-CC-C_6H_4-$, and R^{III} is selected from methyl, ethyl, phenyl, hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, and morpholino; or

- a group -C(O)-heterocyclyl, wherein heterocyclyl is as defined above, and wherein such heterocyclyl group is either unsubstituted or substituted by one or more substituents selected from bromo, chloro, fluoro, methoxy, ethoxy, methyl, ethyl, benzyl, phenyl, hydroxy, oxo, carboxy, and nitro; or

- a group $-C(O)-R^{II}$-heterocyclyl or $-C(O)-R^{II}$-aryl, wherein R^{II}, heterocyclyl, aryl and possible substituents of such heterocyclyl or aryl are as described above; or

R and R_1, taken together with the nitrogen atom to which they are attached, represent morpholino, pyrrolidino, piperazino, N-methylpiperazino, succinimido, or phthalimido;

R_2 is C_3 -C_{15} linear or branched alkyl, either unsubstituted or substituted by a C_3 -C_7 cycloalkyl group; or

R_2 is a group $-R^{II}-H$, wherein R^{II} is as defined above, either unsubstituted or substituted by one to three substituents selected from methyl, ethyl, C_3 -C_4 linear or branched alkyl, fluoro, chloro, C_1-C_4 alkoxy, nitro, amino, dimethylamino, carboxy, carboxymethyl; or

R_2 is a group $-R^{II}-X-R^{IV}$, wherein $-R^{II}-$ is as defined above, -X- is either a direct bond, -O-, -S-, -SO-, $-SO_2-$, -CONH- or -NHCO-, and R^{IV} is either C_1 -C_6 alkyl, C_2 -C_6 alkenyl, methyl, ethyl, propyl, butyl, phenyl or benzyl, the benzene ring of the phenyl and benzyl groups being either unsubstituted or substituted by one or more substituents selected from methyl, ethyl, propyl, butyl, hydroxy, methoxy, ethoxy, chloro, fluoro,

trifluoromethyl or nitro;

R_3 is phenylmethyl, cyclohexylmethyl, isobutyl, tert-butyl, $-C(CH_3)_2C_6H_5$, $-C(CH_3)_2OCH_3$, $-C(CH_3)_2SCH_3$, $-C(CH_3)_2SOCH_3$, $-C(CH_3)_2SO_2CH_3$, $-CH(C_6H_5)_2$, $-CH(CH_3)OH$, $-CH(CH_3)OMe$, $-CH(CH_3)O$-isopropyl, $-CH(CH_3)O$-tert-butyl, $-CH(CH_3)OPh$, $-CH(CH_3)OCH_2Ph$, (4-methoxy)phenylmethyl, (4-hydroxy)phenylmethyl, indolylmethyl, (N-methyl)indolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, (4-carboxymethoxy)phenylmethyl, cyclohexyl, phenyl, pyridyl, thiazolyl, thienyl, pyridylmethyl, thiazolylmethyl, thienylmethyl, and derivatives thereof wherein any phenyl, pyridyl, thiazolyl and thienyl group is substituted by chloro, fluoro, methoxy or C_1 $-C_3$ alkyl;

R_4 is either O-alkyl, wherein alkyl is a C_1 $-C_4$ straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 $-C_4$ straight or branched alkyl, chloro and methoxy; or

R_4 is $-NH_2$, or -NH-alkyl, wherein alkyl is selected from methyl, ethyl, propyl, butyl, isopropyl, iso-butyl, sec-butyl, tert-butyl: such linear or branched alkyl groups being either unsubstituted, or substituted by a group selected from phenyl, benzyl, 2-pyridyl, 3-pyridyl, 1,3,4-thiadiazolyl-2-yl, 2-thiazolyl, these groups in turn being either unsubstituted or substituted by a substituent selected from methyl, ethyl, methoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, ethoxycarbonyl, $-SO_2NH_2$, $-SO_2NHC_6H_5$, $-SO_2$-morpholino, $-SO_2CH_3$, $-CONH_2$, -CO-morpholino: or

R_4 is a group $-NHCH_2CH_2Y$, $-NHCH_2CH_2CH_2Y$, $-NHCH_2CH_2CH_2CH_2Y$, $-NHCH_2CH(CH_3)Y$, or $-NHCH_2C(CH_3)_2Y$, wherein Y is amino, methylamino, dimethylamino, morpholino, pyrrolidino, piperazino, N-methylpiperazino, hydroxy, methoxy, ethoxy, methylthio, 2-(dimethylamino)ethylthio, 2-(morpholino)ethylthio, Cl, F, Br, phenoxy or phenylthio, wherein the phenyl ring may be substituted by hydroxy or methoxy; or

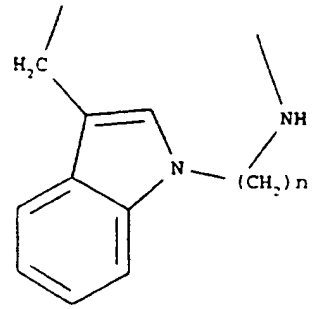
R_4 is a -NH-aryl, -NH-heterocyclyl, $-NH-CH_2$-aryl, $-NH-(CH_2)_2$aryl, $-NH-CH_2$-heteroaryl, or $-NH-(CH_2)_2$-heterocyclyl wherein the aryl group is selected from phenyl, 4-fluorophenyl, 4-methoxyphenyl, 1,3-benzodioxolyl, 4-tolyl, 1-indanyl, 5-indanyl, and the heterocyclyl group is selected from 2-benzimidazolyl, 2-benzothiazolyl, 1-benzotriazolyl, 2,5-dimethyl-1-pyrrolidinyl, 2,6-dimethylpiperidinyl, 2-imidazolyl, 1-indolyl, 5-indolyl,

5-indazolyl, 1-isoquinolyl, 5-isoquinolyl, 2-methoxy-5-pyridyl, 1-methyl-2-benzimidazolyl, 4-methyl-7-coumarinyl, 3-methyl-5-isothiazolyl, 5-methyl-3-isoxazolyl, pyrazinyl, 3-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 3-quinolyl, 5-tetrazolyl, 1-methyl-5-tetrazolyl, 1,3,4-thiadiazol-2-yl, 2-thiazolyl, 1,2,4-triazin-3-yl, and 1,2,4-triazol-3-yl; or

R_4 is -NH(C_2 -C_6 alkyl), wherein the alkyl group is substituted by a substituent selected from -$CONH_2$, -CONHMe, -$NHCONH_2$, -$NHCONMe_2$, -NHCO-(4-morpholino), -NHCO-(4-methyl-1-piperazino), -$NHSO_2NH_2$, -$NHSO_2NMe_2$, -$NHSO_2$-(4-morpholino), and -$NHSO_2$-(4-methyl-1-piperazino); or

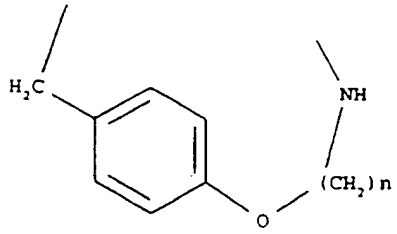
R_3 and R_4 taken together are a group of the formula -$(CH_2)_{10}$-NH-, or a group of the formula -$(CH_2)_4$-NH-$(CH_2)_5$ -NH- : or

R_3 and R_4 taken together are a group of the formula (B) hereinbelow:



(B)

or a group of the formula (C) hereinbelow:



(C)

wherein n is an integer from 3 to 6;

and the pharmaceutically acceptable salts, solvates, hydrates, or prodrug thereof, as above described, with the proviso that, when -NRR_1 is -NH_2, protected amino or acylamino, R_3 is tert-butyl and R_4 is either amino or alkylamino, then R_2 is different from isobutyl.

3. A compound as claimed in claim 2 wherein

R_2 is isobutyl;

R_3 is phenylmethyl:

and W. R. R_1 and R_4 are as defined claim 2.

4. A compond as claimed in claim 2 wherein R_2 is isobutyl:

R_3 is 4-fluorophenylmethyl, 4-hydroxyphenylmethyl, 4-methoxyphenylmethyl; or

R_3 is selected from phenyl, pyridyl, thiazolyl, thienyl, pyridylmethyl, thiazolylmethyl, thienylmethyl, quinolylmethyl, isoquinolylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, indolylmethyl, N-methylindolylmethyl, imidazolylmethyl, including derivatives thereof substituted at the phenyl, pyridyl, thiazolyl, thienyl, quinolyl or isoquinolyl ring by one or two substituents selected from chloro, fluoro, hydroxy, methoxy, methyl, ethyl, t-butyl, -OCH_2COOH; or

R_3 is cyclohexyl or cyclohexylmethyl; or

R_3 is selected from $-C(CH_3)_2OCH_3$, $-C(CH_3)_2SCH_3$, $-C(CH_3)_2SOCH_3$, $-C(CH_3)_2SO_2CH_3$, $-CH(CH_3)OH$, $-CH(CH_3)OMe$, $-CH(CH_3)O$-isopropyl, $-CH(CH_3)O$-tert-butyl, $-C(CH_3)_2CH_2OH$, $-(CH_2)_3OH$; or

R_3 is a group a group selected from $-CH(C_6H_5)_2$, $-C(CH_3)_2C_6H_5$, $-CH(CH_3)OPh$, $-CH(CH_3)OCH_2Ph$, including derivatives thereof substituted at the phenyl ring(s) by one or two substituents selected from chloro, fluoro, hydroxy, methoxy, methyl, ethyl, propyl or t-butyl; or

R_3 and R_4 taken together constitute a group of the formula $-(CH_2)_{10}$-NH-, or a group of formula (B) or (C) above, wherein n is 6;

and W. R. R_1 and R_4 are as defined in claim 2.

5. A compound as claimed in claim 2 wherein R_2 is a C_7 -C_{15} linear alkyl; or

R_2 is cyclopentylmethyl; or

R_2 is cinnamyl, benzyl, (phenyl)ethyl, (phenyl)propyl, (phenyl)butyl, 4-phenyl-3-butenyl, 4-phenyl-3-butinyl, (phenyl)pentyl, (phenoxy)methyl, (phenoxy)ethyl, (phenoxy)propyl, (phenoxy)butyl, (phenoxy)pentyl, (benzylaminocarbonyl)propyl, phenylthio, (phenylthio)methyl, (phenylthio)ethyl, (phenylthio)propyl, phenylsulfonyl, (phenylsulfonyl)methyl, (phenylsulfonyl)ethyl, (phenylsulfonyl)propyl, including derivatives wherein the benzene ring of such groups is substituted, preferably in the para position, by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, hydroxy, methoxy, chloro, fluoro, trifluoromethyl, phenyl, fluorophenyl, methoxyphenyl, methylphenyl, ethylphenyl, propylphenyl, butylphenyl;

and W, R, R_1, R_3 and R_4 are as defined in claim 2.

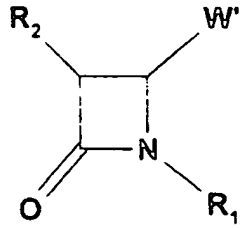
6. A compound as claimed in claim 2 wherein R_4 is either NH-aryl or NH-heterocyclyl, wherein aryl and heterocyclyl are as defined in claim 2, either unsubstituted or subsituted by one to three substituents selected from methyl, ethyl, fluoro, chloro and methoxy; or

R_4 is either O-alkyl, wherein alkyl is a C_1 -C_4 straight or branched alkyl group, especially methyl, ethyl and t-butyl, or it is O-phenyl, and derivatives thereof substituted by one to three substituents selected from C_1 -C_4 straight or branched alkyl, chloro and methoxy;

and W, R, R_1, R_2 and R_3 are as defined in claim 2.

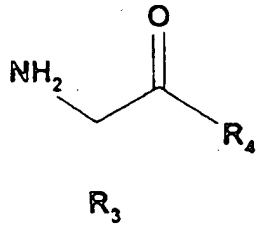
7. A process for preparing a compound of formula (I) as defined in claim 1, which process comprises

(a) reacting a beta-lactam compound of general formula (II):



(II)

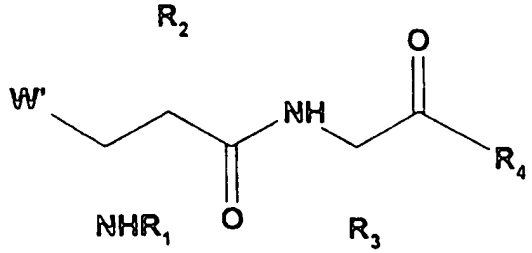
wherein R_1 and R_2 are as defined in claim 1, and W' is either COOH, CONHOH or protected derivatives of the same, with an amine of formula (III):



(III)

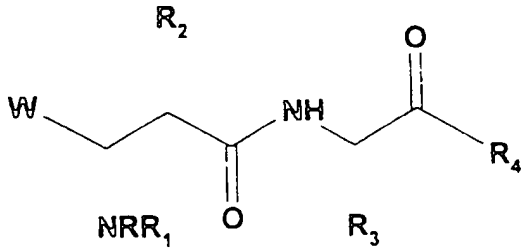
wherein R_3 and R_4 are as defined in claim 1; and

b) converting the so-obtained compound of formula (IV):



(IV)

wherein W', R_1, R_2, R_3 and R_4 are as defined above, into a compound of formula (I):

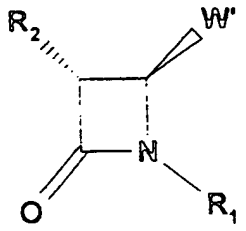


(I)

wherein W, R, R_1, R_2, R_3 and R_4 are as defined in claim 1, and if needed, removing the protecting groups and, if desired, converting any of the groups W, R, R_1, R_2, R_3 and R_4 into different groups W, R, R_1, R_2, R_3 and R_4 at the end or at any stage of the process.

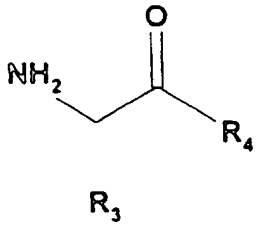
8. A process for preparing a compound of formula (I') as defined in claim 2, which process comprises

(a) reacting a beta-lactam compound of general formula (II'):



(II')

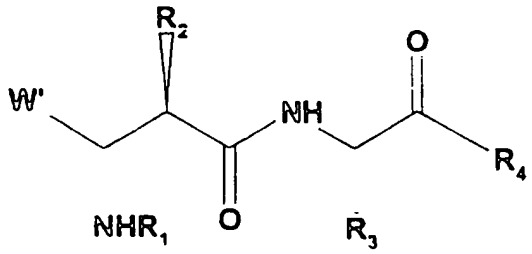
wherein R_1 and R_2 are as defined in claim 2, and W' is either COOH, CONHOH or a protected derivative thereof with an amine of formula (III'):



(III')

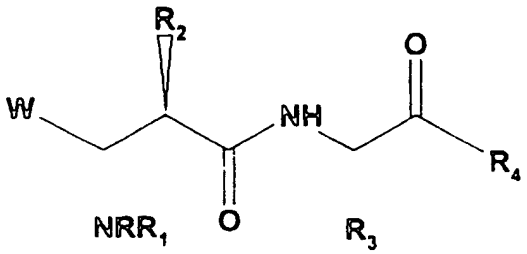
wherein R_3 and R_4 are as defined in claim 2; and

b) converting the resulting compound of formula (IV'):



(IV')

wherein W', R_1, R_2, R_3 and R_4 are as defined above, into a succinic amide derivative of formula (I'):



(I')

wherein W, R, R_1, R_2, R_3 and R_4 are as defined above, and if needed, removing the protecting groups and, if desired, converting any of the groups W, R, R_1, R_2, R_3 and R_4 into different groups W, R, R_1, R_2, R_3 and R_4 at the end or at any stage of the process.

9. A process according claim 7 or 8 for preparing a compound of formula (I) or (I') as defined in claims 1 or 2, which further comrises converting such compounds into their pharmaceutically acceptable salts, prodrugs, hydrates or solvates by means of known reactions.

10. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 7, and a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 97/03251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C259/06 C07C237/22 C07D213/40 C07D213/75 C07D209/48
C07D217/02 C07D277/28 C07D277/46 C07D285/12 C07D295/12
C07D295/18 C07D295/22 C07D307/66 C07D317/66 C07D333/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 497 192 A (F. HOFFMANN-LA ROCHE AG) 5 August 1992 see claims 1,21,26,27,30 ---	1-3,10
A	EP 0 236 872 A (F. HOFFMANN-LA ROCHE & CO. AG) 16 September 1987 see claims 1-3,26 ---	1-3,10
A	EP 0 520 573 A (GLAXO INC.) 30 December 1992 see claims 1-3,12 ---	1-3,10
A	EP 0 489 577 A (CELLTECH LTD.) 10 June 1992 see claims 1,2,7,14 --- -/--	1,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
9 October 1997	29. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

In ...tional Application No
PCT/EP 97/03251

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/08 A61K31/16 A61K31/44 A61K31/40 A61K31/47
A61K31/425 A61K31/335 //(C07D487/08,245:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. R. MORPHY ET AL.: "Matrix Metalloproteinase Inhibitors: Current Status" CURRENT MEDICINAL CHEMISTRY, vol. 2, 1995, pages 743-62, XP002043028 cited in the application see page 745, compound 4; page 751, compound 28 ---	1-3
A	P. D. BROWN: "Matrix metalloproteinase inhibitors: A new class of anticancer agent" CURRENT OPINION IN INVESTIGATIONAL DRUGS, vol. 2, no. 5, 1993, pages 617-26, XP002043029 cited in the application see figure 3 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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2

Date of the actual completion of the international search
9 October 1997

Date of mailing of the international search report
29. 10. 97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

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Hass, C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/03251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ²	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	J. R. PORTER ET AL.: "Recent developments in matrix metalloproteinase inhibitors" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 5, no. 12, December 1995, pages 1287-96, XP002043030 cited in the application	1-3
A	N. R. A. BEELEY ET AL.: "Inhibitors of matrix metalloproteinases (MMP's)" CURRENT OPINION IN THERAPEUTIC PATENTS, vol. 4, no. 1, January 1994, pages 7-16, XP002043031 cited in the application	1-3
A,P	A. H. DAVIDSON ET AL.: "The inhibition of matrix metalloproteinase enzymes" CHEMISTRY & INDUSTRY, no. 7, 7 April 1997, pages 258-61, XP002043032 cited in the application see page 260, figure 3	1-3
A	R. P. BECKETT ET AL.: "Recent advances in matrix metalloproteinase inhibitor research" DRUG DISCOVERY TODAY, vol. 1, no. 1, January 1996, pages 16-26, XP002043033 cited in the application see page 19	1-3
A	P. A. HILL ET AL.: "Inhibition of bone resorption in vitro by selective inhibitors of gelatinase and collagenase" THE BIOCHEMICAL JOURNAL, vol. 308, 1995, pages 167-75, XP002043034 cited in the application see page 170, right-hand column, compound CT1166	1
A	A. KRANTZ: "Proteinases in inflammation" ANNUAL REPORTS IN MEDICINAL CHEMISTRY, vol. 28, 1993, pages 187-96, XP000650773 cited in the application see page 193, compound 16	1
A	US 4 599 361 A (J. P. DICKENS ET AL.) 8 July 1986 cited in the application see claim 1; examples	1

2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In ...tional Application No
PCT/EP 97/03251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 497192 A	05-08-92	AU 658387 B	13-04-95
		AU 1025792 A	06-08-92
		BG 60794 B	29-03-96
		CA 2058797 A	02-08-92
		CS 9200201 A	12-08-92
		HU 9500229 A	28-08-95
		JP 4352757 A	07-12-92
		MX 9200282 A	01-08-92
		NZ 241409 A	27-06-94
		SI 9210090 A	30-04-95
		US 5304549 A	19-04-94
EP 236872 A	16-09-87	AU 588437 B	14-09-89
		AU 6990287 A	17-09-87
		CA 1314655 A	16-03-93
		DE 3782751 A	07-01-93
		DK 77487 A	12-09-87
		IE 60128 B	01-06-94
		JP 1902991 C	08-02-95
		JP 6029228 B	20-04-94
		JP 62230757 A	09-10-87
		US 4996358 A	26-02-91
EP 520573 A	30-12-92	AU 1864092 A	07-01-93
		CA 2072551 A	28-12-92
		JP 6025284 A	01-02-94
		MX 9203643 A	31-01-95
		US 5252560 A	12-10-93
EP 489577 A	10-06-92	AT 120182 T	15-04-95
		AT 120451 T	15-04-95
		AU 652793 B	08-09-94
		AU 9017391 A	25-06-92
		AU 652596 B	01-09-94
		AU 9023391 A	25-06-92
		CA 2073510 A	04-06-92
		CA 2073513 A	04-06-92
		DE 69108363 D	27-04-95
		DE 69108363 T	31-08-95
		DE 69108529 D	04-05-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/03251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 489577 A		DE 69108529 T	30-11-95
		EP 0489579 A	10-06-92
		ES 2069833 T	16-05-95
		WO 9209564 A	11-06-92
		WO 9209565 A	11-06-92
		GB 2255339 A,B	04-11-92
		GB 2255340 A,B	04-11-92
		HU 61973 A	29-03-93
		JP 5503719 T	17-06-93
		JP 5503720 T	17-06-93
		US 5300501 A	05-04-94
		IE 70429 B	27-11-96
US 4599361 A	08-07-86	AU 588362 B	14-09-89
		AU 6240886 A	12-03-87
		CA 1329397 A	10-05-94
		DK 169029 B	01-08-94
		EP 0214639 A	18-03-87
		IE 58770 B	03-11-93
		JP 2029563 C	19-03-96
		JP 7064800 B	12-07-95
		JP 62103052 A	13-05-87
		US 4743587 A	10-05-88